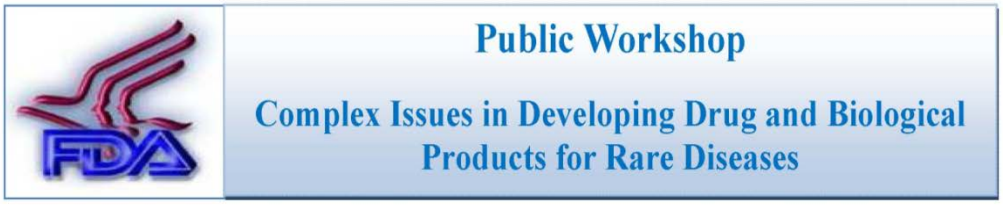

"Complex Issues in Rare Diseases Drug Development"

PUBLIC AGENDA- DAY2

January 7, 2014

FDA White Oak Campus

(Silver Spring, MD)

Session Six
Networks and Collaborations in Support of Pediatric Clinical Trials

Dianne Murphy: I wanted to welcome you all this morning. My name is Dianne Murphy, the Director of the Office of Pediatric Therapeutics at the FDA and with the help of many people, including the rare disease group here at FDA, we are putting together a meeting where we want participation and input in a vigorous manner. For those of you who were not here yesterday, this is going to be the last sslide you will see today.

Slide: Pediatric Rare Diseases: Day 2 Goals

1) Learn from our past experiences
2) Bring forth ideas for further discussion
3) Promote development of Data to validate pediatric endpoints for pediatric rare diseases
4) Promote development of Methods for long term assessments in a pediatric population which is developing
5) Enhance development of pediatric Networks
6) Enhance discussions on Risk among regulators, parents, patients and investigators
7) Support increasing availability of Data – consider need of "layering" specificity of data to address privacy issues.

There will be no more slide presentations or slow death by Power Point. We are going to have sessions that will be in the control of the session chairs; they are going to keep track of the speech timing, not the content of each individual. I think they are limited to around three minutes. I understand they can get pretty precise on this, because we want to have at least 45 minutes or more of discussion at each session. We have encouraged the audience to participate; we've taken down the stanchions, we've moved the mikes, so we hope that you have access to them.For questions, we have Terrie Crescenzi, who will collect questions from you; or, if you prefer to come up to the mic, that's fine; if you wish to turn the written questions into her, that's fine, but we really are counting on your participation.

The introduction that I'm supposed to give, I hope to get through pretty quickly, so that we can get to the meat of this session. We are here today because of the issues surrounding trial designs and the conduct of pediatric trials in general. When putting thoughts together for this, really all we have here with rare diseases is even a larger problem because of the smaller numbers. Yesterday many people talked about the tyranny of small numbers. And that is really the main problem we have in multiples when we're dealing with rare diseases within the pediatric population. So the themes that you hear today are really themes that are very, very familiar to those of you who work in pediatric research or pediatric product development.

They ended yesterday with something I think we should begin today with and Anne Zajicek has gallantly taken on this task, which is we do some of our best learning from not only our past experiences but from our past mistakes. One of the goals that we have here at FDA in pediatrics is to publish information on negative studies. And because of the problems we have in pediatrics, we have a high number of failed product development trials, why is that? We need to figure that out. We already know some important lessons from this: dosing, endpoints, being able to maximize our ability to see the effect size,, all of these are issues in pediatric studies, and Anne is going to go over with us many of the experiences we have.

We are now at over 10 years of asking NIH, NICHD to help us get some of the products that industry is not interested in studying, getting them studied, and they now have a decade's worth of experience in working with us. Today we'll be going over some of the issues that we have learned from these experiences.

We hope today also to bring forth ideas for further discussions and, as they like to say, that is no stupid idea, bring it forth, we want to hear it. We may not use it but we certainly want people to feel free to bring forth ideas. We want to promote the development of data and development of data to validate pediatric endpoints for pediatrics in general and particularly for pediatric rare diseases. We're struggling with neonates and how we develop endpoints for them. This is an enormous area of development for FDA.

We want to promote development of methods for long-term assessments of a population, which is developing. Listening yesterday to the adult discussion on the adult issues with rare diseases, in pediatrics, one can see again, we have the multiplier of an evolving and developing organism, that's going to change over time, so having these natural history studies in a developing organism is another layer of difficulty for pediatrics.

And of course, one of the big issues is enhancing the development of pediatric networks. Europe has mandated this, they are doing it, and we in America need to be part of this because we need to – pediatric trials are global. We need to enhance the discussions among the regulators, parents, patients and investigators on risk, and you are going to have the entire session on risk assessment today and we hope you'll be very active participants in that discussion.

We want to support the increasing availability of data to the public. Yesterday we heard a lot about the concerns of privacy particularly with genetic coding, and I think we need to talk about layering our specificity of data. A problem with one set of data should not limit the access to the rest of the data, and this is my comment. Maybe children should not even enter a trial if the data will not become publicly available to inform future trials. The legislation that the American Academy of Pediatrics has worked for decades to put in place, along with many other pediatric advocates, has basically put this postulate into action. If the trial is conducted under the pediatric legislation of either BPCA or PREA to be submitted to FDA, in other words, it's conducted in

response to some of the legislation that's been passed to encourage it or to require pediatric studies, those negative studies need to see the light of day in our labeling.

Now some of you who are not big aficionados of FDA may not think that's important. However, it is a major issue and an important step forward. Even if we can't put all the information in the label about that negative trial, there is a review and it will be available to the public on what that trial was about, how many kids were in, what the endpoints were, etc. For Children who are participating in trials, and again we heard a lot about this yesterday in general but particularly in pediatrics, this is very important. Why?

Unlike adult product development where if they fail, they have an incentive to study it again until they get the dose right, until they get that endpoint refined, until they get that population identified that's going to respond, there is not that incentive for pediatrics, and there will not usually be subsequent studies. So, the data from that pediatric study maybe the only data, unless we have a way of incentivizing or requiring additional studies. And that's why it becomes important that pediatric study data become publicly available.

Slide:

Overarching topics,: , in hope of increasing the likelihood of a productive workshop, we have focused on the following major areas, but they are not to limit your discussion.

Pediatric trial development issues-what we've learned and the need for networks

Risk assessments for pediatrics

Specific issues with oncology and gene therapy.

If you will notice the agenda today, we have these specific areas as Topics. . We e think specific examples of areas help people focus and get into the pragmatics of the issues, and so we've attempted to do that for you.

Yesterday, I was talking about the breakthrough therapies and the lessons learned from why they failed. And I think there are many of the similar lessons that we have from pediatrics. In that sometimes people want to take historical data and use that, that we can do that, but it has to be very vigorous, we have to able to review it. The bottom line is that we need data and we need to be able to quality control it, we need to be able to verify it, and we need to be able have confidence in it.

So I think the last bullet there was the summary from yesterday, sometimes the data that's being presented to FDA is really more triumph of hope over evidence, and I think this is something that we need to deal with. We have in pediatrics an additional area, in which we use other prior

knowledge and its adult data, we use adults as our – not our preclinical but some of our prior knowledge, but that data needs to be explained as to how you are going to use it to extrapolate to pediatrics, and you have to have good science behind that to be able to do that.

So the process, as I told you, the Chair is going to be responsible for keeping the session on time, and this is 50 minutes, it's at least 45 minutes for audience participations. I told you about the questions, I encourage you to participate, and I'm going to introduce Anne Zajicek, who is our major liaison at NICHD, and I'm going to ask her to introduce herself and her panel, and she will be in charge of running this session. We'll hold her responsible for getting you to participate, and for the committee, our panel for having an active discussion. Each panel chair has that responsibility and they will also be responsible for keeping us all on time.

Thank you for coming and I'm very glad to see everybody's car or metro worked today or planes and got you here, and we very much look forward to your discussion. Anne, it's all yours.

Anne Zajicek: Good morning. Thank you all for sitting up close because the game plan here is that we have about 12 panelists, they are going to speak for about 180 seconds each, and then after we are done talking for a maximum of 45 minutes, the purpose of this was to have people speaking, to have communication, to have discussion about your experiences with networks, what's worked with you, what hasn't worked, and specific questions for our panelists as well. So we appreciate you sitting up close and we look forward to some active discussion.

So why am I chairing this network question? So I am the Chief of the Obstetric and Pediatric Pharmacology and Therapeutics Branch at National Institute of Child Health and Human Development, the branch has been in existence since 2004, and it started mostly because of the legislation to improve pediatric labeling. So in 1997 there was the FDA Modernization Act, in 2002 the Best Pharmaceuticals for Children Act was passed, and it's the responsibility of my branch at NICHD to implement the Best Pharmaceuticals for Children Act, the NIH part of it.

Now the issue about the legislation was what was nice about FDAMA is that there was a provision for another six months on the patent life of a compound if appropriate pediatric labeling information was submitted to FDA, it could be positive data, it could be negative data either way, but if it was consistent with FDA policy and what FDA requested under the written request. So as you know, I am a pediatrician and a lot of people in this room are pediatricians, there is a lot of drugs that are off label, and so therefore there is no six-month exclusivity on a product that already doesn't have a patent life.

And so the NIH was tasked to do three things under BPCA: Point number one was to prioritize drugs in the 2002 legislation and then when it was reauthorized in 2007 and 2012 to prioritize therapeutic areas and then drill down into what drugs were lacking pediatric labeling and should be studied, and I'll get to where we are in a minute for that.

Our next job was to sponsor those pediatric clinical trials. Now initially, we did not have a network set up for that. What we had done, because the initial round of legislation had asked for us to put out contracts to do these clinical trials was to put out request for proposals or RFPs, which are listed in the FedBizOpps, that's how the government does its contracting business, and then to award contracts for individual clinical trials for labeling purposes for various drugs.

And the drugs that we studied under that process included drugs that you'll be surprised lacked pediatric labeling because they are being used all the time, include lorazepam or Ativan for sedation, lorazepam for status epilepticus or Baclofen for spasticity, nitroprusside for blood pressure reduction, lithium for acute mania in children with bipolar disease, as I mentioned hydroxyurea previously for sickle-cell disease.

We partnered with the Children's Oncology Group and Dr. Greg Reaman and Dr. Peter Adamson to look at vincristine, Actinomycin D, daunomycin, methotrexate, isotretinoin. So these are all clinical trials that are either completed or ongoing. Now just to let you know what the process is, so we had in the case of nitroprusside, which is the one that's I think closest to labeling. If it doesn't have a label now, it will in the next few days.

We performed the clinical trial as requested by FDA, and there were negotiations and they were about how the protocol would look, the number of patients, how the protocol was written, and then the data are submitted to the FDA Review Division. And then there is discussion in the FDA Review Division about whether we did in fact complete the trial that FDA had requested, then those data are de-identified and they are submitted to the FDA docket. So the legislation was very specific about making sure that the data that the NIH was generating was publicly available. Now the dockets are little funky but you can find all of the data that we submitted to the FDA Review Division in the FDA docket as announced in the Federal Register.

So those data are public and then they are reviewed by the FDA Review Division and then during the 180 day period between when the data is submitted to the docket, and the 180 days the FDA Review Division reviews the data and then negotiates with the NDA or abbreviated NDA or the – in other words the generic manufacturer for the labeling change. And I believe December 20th there was a Federal Register announcement there had been some preliminary back and forth and a preliminary acceptance of labeling changes for nitroprusside, and I believe that we are waiting for a final Federal Register announcement.

But anyway, so that's the flow of this. Now what we learned in the meantime was that having a contract for a specific academic investigator was not necessarily the right way to go about doing this because what we found is in the middle of trials that we needed a research formulation but there wasn't anything in that RFP in the contract to mandate that kind of work, so there were pieces of the puzzle missing. So what we thought might be a better plan of attack is to put out another contract proposal for a clinical trials network. And that was awarded to Duke University

in 2010, I believe, with Danny Benjamin who will be speaking in a minute, which would fulfill sort of the whole ball of wax here.

So in another words they would be able to manage the clinical trial to make sure that recruitment was appropriate, that the clinical trial was moving along at a reasonable pace, and if some of the clinical trial sites were not able to recruit, for example, that they would be replaced with other sites. Again the research formulation was a problem for a couple of clinical trials we had, there was a need for assay work, which sometimes requires outside labs, protocol development, pharmacokinetic, pharmacodynamic modeling, protocol development, those kinds of tasks. So when we were thinking about what would be everything that we would need to do a clinical trial, again put those, that information into that request for proposal.

Now the other thing that's critical and the reason that I'm so glad that you all are here is that, again the three tasks of the NIH part of BPCA are number one to prioritize therapeutic areas, number two to sponsor clinical trials and number three to submit these data to FDA for labeling changes. This issue of prioritization is key for us because what we're looking at is medications that are used either frequently or not frequently, and we've had a lot of discussions about exactly what to prioritize. Should we be looking at frequent conditions such as asthma and otitis media? Should we be looking at infrequent conditions, such as the rare disorders that we've been talking about over the last day? Should we be talking about pediatric cancers?

So we are having a mix of areas but we request public input in this prioritization process, so if there is specific drugs, therapeutic areas that you feel are lacking, we would be more than happy to include those in our prioritization process and consider performing a clinical trial, however we best could. So just to let you know, we are looking for that kind of information, so feel free to talk to me here, however you want to get in touch with me, call me, email, what have you.

So I think that that was all I had to say, and now I'd like to introduce our panelists. So our panelists and I really, really appreciate people coming in and going out of their way to attend this, is a mixture of government, heads of networks, internal to NIH, as well as patient advocates. And then after – I'm just going to state their names and the organizations they are responsible for then we'll go around the table and they'll each speak for a few minutes. And then at that point I would like to go through the questions that we'd like to review today, and then we would like to have again a lot of interaction with our group.

So our panelists this morning include Danny Benjamin, who represents the Pediatric Trials Network; Dr. Ed Connor, representing the Clinical and Translational Science Awards; Dr. Gail Pearson, from the National Heart, Lung and Blood Institute, representing the Pediatric Heart Network; Elizabeth McNeil, from the National Institute of Neurological Diseases and Stroke, representing the Neuro-NEXT network, which was mentioned yesterday; Dr. Steven Hirschfeld, will be joining us shortly.

Oh, he is here, thank you, Steven, I apologize, hello. He is our Associate Director for Clinical Research, NICHD as well as the Head of the National Children's Study, and he will be discussing Global Research in Pediatrics, GRIP, and other EU initiatives; Dr. Jonathan Goldsmith from the National Heart, Lung and Blood Institute, representing the Sickle-Cell Disease Consortium.

Our outpatient care representatives include Katie Clapp, representing FRAXA, the Fragile X Research Foundation; Betsy Peterson, the Children's Heart Foundation; Robert Beall, from the Cystic Fibrosis Foundation, Cynthia Le Mons of the National Urea Cycle Disorders Foundation; Jana Monaco, from the Organic Acidemia Association.

So I've sort of randomly grouped these into NIH networks which are disease specific, NIH networks non-disease specific, EU, discussion of devices in particular, our two specialists include Dr. Gail Pearson and Betsy Peterson. And in the advocacy area: Katie Clapp, Cynthia Le Mons, Robert Beall and Jana Monaco. So why don't I start with Jonathan Goldsmith, if you don't mind, he could give us some information about your sickle-cell networks.

Jonathan Goldsmith: Am I live? Yes. So good morning, again thank you very much for asking me to sit in today to represent sickle-cell disease. I'm a Program Officer at the National Heart, Lung and Blood Institute, which means I do a lot of day-to-day work in terms of how studies are organized and conducted. And also I'm a hematologist, I am actually trained as an internist but I've practiced pediatrics for many decades. And I have a career long investigational interest in rare diseases across the spectrum of diseases from clotting disorders to hemoglobinopathies and inherited lung disease etc.

I wanted to just talk about a couple of different aspects of this building of networks if you will, because it includes a professional side, an academic side, a medical investigator side of things. There is also the patient and family side of things that has to be encountered as well and dealt with. So just a few bullets so I can keep this short. We need an investigator commitment to the process and outcomes, I wrote down, and I think that's really critical.

A lot of people say they want to do research but they don't put the time aside for it and at the end of the day things don't work very well. I think that's a critical issue. You need a cadre of well-trained investigators and research teams. You need institutional support from academic side, which means space personnel and financial support. You need linkage to stakeholder organizations, and it has to be more than just, I know there is an organization in my town, there has to be some evidence for what the interaction is.

There has to be available non-coercive subject incentives and travel support for study visits. Lots of patients and families need this kind of access to clinical trials. And in your academic side or your clinical side, you need to have a large enough patient population to actually support the

clinical trials. Having a single subject in a disorder where there is tens of thousands of people, still rare disorder, is probably not sufficient to have a clinical site there, and I've gone through the difficult process more than once in closing sites because of failure to enroll. It was not the best investment.

From the patient and family side, we have to consider, things especially in sickle-cell I think, there is socioeconomic status including diminished access to technologies, we are all linked very well, social media and so on now, but that may not be available to everybody. Race and discrimination is a big issue. I think it's something that has to be dealt with in a straightforward manner, and that we have to accept that is a problem of the past but one that we need to make better and to make access available to people and offer trials that are available. Sickle-cell disease is a complex multi-organ disease, it's not just a missing protein, it's a simple genetic defect, but it results in a catastrophic disorder that affects brain, heart, lungs, kidneys etc.

The family structure is important in terms of patient family participation. We deal with a lot of nontraditional families and there are lots of issues that come up around who can give consent for that child participation, what really is the legal network. Geography and transportation are a problem, and not just in rural areas and urban areas as well. Getting across a city like Los Angeles is almost impossible, I think as many of you know.

Health literacy is important, there has to be effective communication and understanding of medical terms and directions. If you think about the Affordable Care Act which some of us if had a chance to look up on the web a few times, you can see that there is a whole new set of terms and acronyms. How do you understand half of this stuff? How do you actually relate to people? How do you talk to people from different socioeconomic strata with different kinds of educational background? It's critical stuff.

In terms of sickle-cell disease in specifically the African-American population, there is an issue of trust; there is the heritage of Tuskegee. We deal with this, it's real, it's transgenerational, it doesn't go away. These are critical things in terms of organizing a network, getting participation, having people understand why this is different, has there been full disclosure.

There is also phenotypic variability in sickle-cell disease, so a lot of young children are not very sick, and so people don't want to be in clinical trials where they take drugs that maybe were used for cancer before. It's another kind of an issue. How do you actually predict who will be sick soon? There is also the complexity of trial designs, and follow-up requirements. Lots of people want to have secondary endpoints, do other kinds of studies, do nested studies, and it really is almost impossible to do, I think in these kind of difficult disorders, to try and get all of that information at a one little study becomes very difficult.

So let me tell you a couple of successful networks and then I'll be done, that we've done for children with sickle-cell disease. These were a couple, the landmark study was called STOP 1 and STOP 2, it was a randomized trial to evaluate whether chronic transfusion could prevent initial stroke in children with sickle-cell disease at high-risk based on determination of a Trans cranial Doppler, which is a measurement of blood pressure that's in the brain.

It demonstrates a large benefit, it was halted early. And it was done under a funding mechanism that we call a cooperative agreement, where there is some NIH input into the trial design and conduct. It was conducted in children 2 to 16 years of age at 14 clinical sites. They screened over 1900 people to actually find the 160, who are ultimately enrolled and randomized, so it's a big operation just to find the number of people that you had to identify and then determine the ones who are most at risk. So those are pretty instructive aspects of that trial.

BABY HUG is another study, it's a double-blind placebo-controlled trial to determine if hydroxyurea treatment is safe, protects spleen and kidney function and improves clinical and laboratory findings. This was also fairly complicated to put together, it took many years to get off the ground, it's conducted under an IND and the National Heart, Lung and Blood Institute is a sponsor of the IND. It was done through a contract mechanism so that we could deal with the individual clinical sites as well as the data coordinating center.

This had a couple of interesting aspects to protect patient safety, each clinical site had ombudsman appointed who is not part of the study but knowledgeable about the study and the risks and benefits, and was available to all patients and families. In addition, through agreement with the FDA, there was initial safety pilot study in the first 40 subjects for toxicity only, so it was a ramp-up kind of study.

Very young children were studied, 9 to 18 months of age at 13 clinical sites. This was much better, 233 were screened, and ultimately 193 were randomized, so this was much shorter path, actually finding the numbers, but it took a long time because typical accruals are about 0.3 subjects per clinical site per month. They are really quite low. There are two follow-up studies that are conducted, that are of observational nature, and they will continue until 2016 and hopefully have a structured follow-up of these children who participated.

We hope that one of the outputs of the follow-up studies is to actually get the data together to apply for pediatric labeling for the use of hydroxyurea in very young children with sickle-cell disease. And papers have been published from these studies that are supportive but we're going through the regulatory process that Anne just described.

So that was just a quick overview of kind of issues that we see from our perspective with a rare disease, not as rare as many represented here today, I understand that, but it is still a rare disease

and it has some unique aspects that have to be dealt with, as you put together a network or you put together a patient advocacy etc. So thank you.

Anne Zajicek: Thank you very much. Next Dr. Elizabeth McNeil.

Elizabeth McNeil: Hello, I'm Elizabeth McNeil, I'm actually a pediatric neuro-oncologist by training, so I have moved to the National Institute for Neurologic Disorders and Stroke to work on your Neuro-NEXT project, which I hear that some of you heard about yesterday.

Sure, I'm from New York, amazing that I'm not audible. Anyway it might be the cold air, the neurologic disorders – NINDS decided that not enough attention was being paid to diseases in neurology and people were getting out of the therapeutic area because it's so hard to do studies in neurologic diseases, so what NINDS want to do was set up a network to try to facilitate studies being done in neurologic diseases. What we did was we set up a network of 25 geographically distributed sites throughout the US along with a data coordinating center and a clinic coordinating center, so that would have an infrastructure in place to do almost any type of neurologic trial.

We have wide breadth, not every center is good at everything but we have with our 25 centers, which are available for those of you who are interested at www.neuronext.org. Put the www in because we also used to get something from GoDaddy and we really don't want to send you there, we want to send you to our website.

Anyway, we decided to do this. And our first project was actually NRA diseases in spinal muscular atrophy, which is a rare condition that you may have been hearing more about it. What we wanted to do was, we knew that there were some therapeutics that were going to be looked at in therapeutic trials coming down the road. However, there are many, there are four different subtypes of SMA, and we were most interested in the infants, and we decided to setup a biomarker only study hoping to get information that could be used in future therapeutic studies.

So we embarked with our very new network on a biomarker trial to enroll infants from zero to six months of age, and we decided just because that wasn't difficult enough that we wanted to add in an investigational device. So we said, oh, this sounds like a lovely idea to begin, and we'd like to use a lot of taxpayer money to do this, and indeed we did. And we started on September 2011, the network was launched, actually it was October 1st because the fiscal year ended. And then we said, let's go forth, and we are going to take a junior investigator who has never had any NIH grant, okay now we are ready.

And it's working. It's actually working with our infrastructure. We are very proud to say that we were told really you're going to get people to bring their kids in, because we had to have a control group and kids with SMA because the natural history of SMA has changed as medical

training and medical techniques have improved, the natural history for what happens in those infants has changed. So therefore we had to have sort of a – we didn't truly want to use historical controls, we wanted to use current controls. So we said, let's get kids now and get kids with SMA so we can do the comparison and have good data to try to validate some biomarkers.

We want to look electro-physiologic biomarkers, we want to look at blood biomarkers, and we said, "Can we do this?" And we were able within the first year that the study started to enroll all of our controls a year earlier than we thought we would be able to, so all the controls are there. We have to wait for babies with SMA to be born. One thing that we did when we setup the network before we even launched the study was we involved patients. As I told you I was trained in pediatrics, the people who know best what's going to be important for the patients and their families are patients and their families. In this case as I told you was babies from zero to six months. They don't have a lot to say, so we asked the parents and caregivers to give their opinions.

And we had parents and caregivers sit on the actual protocol development working groups, and we have that for all of our studies. Within the network you have a parent who is there from the very beginning to give input on how the study is being set up, even things such as how are you setting up the study visits, what breaks are you setting in. We actually, the mom for her SMA study, when all of our nice academics were saying, "Oh, we are going to have those babies come in at 8 in the morning, and then we can give them a break at 12." The mom said, "Right, that's not happening." Infants they need to eat, they need to sleep, they need to take care of the stuff you put in, it has to be cleaned up, always coming out the other end.

All these things have to be taken into account, eight hours of testing is not going to work, you need to incorporate breaks, and you need to actually think about the fact that most people with children have other children, so therefore really should have to come the night before. We said, oh, okay, and she got it changed. She basically said this is what you need to do and we changed the protocol around, changed the study visits with her input because she was our liaison to the advocacy community and she got them onboard, and actually a lot of the control patients have been families who have known someone with SMA or families who have lost a child to SMA.

That I think that was new for NINDS networks to actually insist that a patient or a caregiver is actually embedded from the very beginning of protocol development. And stays so they were in the beginning before the application comes in, and then they stay on it throughout the entire study. I mean obviously we try to keep a patient or patient advocate on the entire time, so that's one thing that we've done that we think is relatively novel, and for at least for an NINDS and it's worked really well.

Then we also involve the advocacy groups and actually advocacy groups for all the studies only have one pediatric study, that's the SMA study at the moment, but for our two adult studies we

have gotten a lot of support from advocacy groups who have beliefs because they have been involved from beginning in what we were doing and then given both financial and in-kind support. I think that's something else that as people become more aware of, and I think it really helps with the recruitment and retention because there is no point in doing a whole study and trying to setup a network unless you have buy in from people who actually hope to benefit.

The geographic distribution issue is something else about Neuro-NEXT that I think was very important because you've heard the discussion about actually getting patients to where the study is being conducted. In very rare diseases we've worked with advocacy groups to find out where the patients are. We haven't avoided any HIPAA type arrangement difficulties because what we do is we just get numbers to figure out, well, how can we get, where which sites would be best to be able to get access to the patients? And that's actually worked. When we set up a geographic distribution, we looked at where people were located in the US. And then decided, okay, which centers can we pick that we can get people to within of about 600 miles based on population density in the US.

We had been very pleased with the way it's works, we should point out that it's open to all, and we actually have a number of rare diseases, and have rare disease advocacy groups that have approached us to see if they can get studies done in their particular condition. And we have been working with them, I think you may have heard about some yesterday, and we hope to continue.

One other thing that we require is for very rare diseases, especially in pediatrics that our applicants work with the FDA early to make sure that the study that they plan is something that would be suitable for regulatory review, because if it is not suitable for regulatory review, even if the therapeutic actually works or the biomarker has a chance to be validated. If the FDA says this study has a flawed design, that makes it worthless and is not a good investment of taxpayer money, so we don't want to do that.

We have worked with Anne with BPCA because there are some overlapping areas, so we try to keep her informed when pediatric studies come in usually by email or frantic calls, and that's worked well. And with that I think there is not much more I can say about the network except that we are very eager to continue working on pediatric rare diseases, which have a special place in my heart, and since I'm the one who all the proposals come through. I do have a particular interest in seeing more come through.

Anne Zajicek: Wonderful, thank you so much. And we'll expand on some of these as time goes on this morning. Let's see, could I have Danny Benjamin speak next about the pediatric trials network and Duke's infrastructure.

Daniel Benjamin: Thanks, Anne. I'm Danny Benjamin, I'm Professor of Pediatrics at Duke's and I lead the pediatric trials network, which is available online, and it's funded by taxpayer

dollars and I'm grateful for that. One of the nice things about the Pediatric Trials Network is that we can compare our metrics to the prior trials that had been done under the BPCA mechanism. Currently our network is getting up one project every other month; most of these projects are clinical trials that are compliant for submission of the data to FDA.

The trials and projects to date are on time and on budget. We are enrolling at approximately six times the rate of the prior BPCA funded trials. We are getting up about, trials about six times as fast as the prior mechanism without the network and we are enrolling patients in and acquiring samples in completing clinical study reports for FDA at between five and eight times the rate at which they were done without the network.

So in short the network is doing what it was designed to do, which is to facilitate enrollment and facilitate completion of trials, which is a great theory. Most of the time networks fail to do that, they tend to fail to do that because of bureaucracy, lack of unity, disorganized agenda, and really the way authority flows down from the funding sponsor through the leadership of the network to the folks who are actually doing the work.

So one of things that we try to get right with the network right away for the leadership team was, we wrote into the application to you guys that the leadership team was not going to be allowed to lead any of the trials, we weren't going to allow any authorship as first and last authors, we weren't going to be allowed academic credit, and by the way we had to give away all the money. And that's really working, because what the leadership team is able to do is set the agenda and enforce the agenda, and it's a very nice delegation of authority from ultimate authority, which is the taxpayer dollars, public health to NIH and FDA to the leadership of the network, and to the people who are doing the work.

I noticed Kathleen Neville is here, she is the leader of one of our hydroxyurea trials, the first words out of her mouth when she saw me this morning was, "The first draft of the CSR has been written." And it's great, so a week early, good, it's good stuff. I think the other things that the network has been able to do is to facilitate common contracts, master service agreements on contracts, which is a study killer as far as startups is concerned. I think the combination of operational – and Anne I'm sorry here I'm two seconds over, I'm going to go about 45 seconds over.

The combination of operational and leadership of the study expertise together, because so many times the monitor's capability as far as the therapeutic area is concerned is just being able to read the inclusion exclusion criteria of a protocol. And they don't really know the disease, and the problem with the very famous world-famous investigator is they've actually never done a clinical study, so they can tell you all about the metabolism but they can't actually tell you how to get the job done.

And then if you are able to partner thought leadership with operational expertise, I think that's been a huge success of the network. And I think finally the pediatric trials network has been unified in a primary purpose to get labeling done for children. And a lot of times I see networks, we get a lot of conference calls and a lot of talking go on without actually being unified, on where is the ship going, and how we are going to get there as fast as possible. And, Anne, I apologize for running a minute over.

Anne Zajicek: Perfect. Thank you very much. Let's see. Could we talk about devices and the work of the Pediatric Heart Network and Children's Heart Foundation next? Gail, would you like to start?

Gail Pearson: Sure, thank you, and thanks for the opportunity to be here and representing NHLBI. When I was in pediatric cardiology fellowship, pretty much all the care we were giving, my mentors told me was based on eminence and not evidence. And so when I went to NHLBI, I wanted to do something to change that. Unlike adult cardiovascular disease where there is a well-established clinical trials infrastructure, this was not the case in pediatrics. And even though it's the most common birth defect, congenial heart disease is still sufficiently rare that at even big centers there are not enough patients to do single center studies. So in 2001 NHLBI launched the Pediatric Heart Network.

We have nine sites, including one in Canada and a number of other sites that help us with specific studies. To date we are about to complete our fourth Phase 3 trial, and we've done a number of other prospective studies in areas where we weren't mature enough yet to do a trial. We have the same problem, everyone else does with endpoints. Like everything else in pediatrics, it takes a village, so we've been pleased to partner with the FDA not only in a regulatory partnership but also through the rare diseases group and we are part of one of the FDA pediatric device sites.

We've also partnered with The Children's Heart Foundation. Thank you, Betsy, and the National Marfan Foundation as well as pharmaceutical companies who've donated drug for us. One of our ways that we've tried to work with families, we realized early on that not only our families particularly when they have a newborn with complex congenital heart disease, they have to monitor – they have to learn the lingo of congenital heart disease but then we are approaching them about a clinical trial. And as you know, clinical trials have their own language that's arcane, so we in collaboration with our data coordinating center that the Child Health Institute has developed the children in clinical study site.

This is a web-based site that we host that's available at the seventh grade level, it's available in English and Spanish, and it helps families understand what it means to be in a clinical trial, what questions they should ask? What they should expect and has some documentary footage including families who decided not to be in trials. And this is a – we don't quite get the number

of visits that Zappos gets but we get about 15,000 visits a month, which we think is pretty good for this kind of site.

We are moving in some new directions, we are going to – we are in the process of conducting a quality improvement study to try to harmonize care across sites in certain areas and improve outcomes. We are moving into some Phase 1 and early Phase 2 studies, and in fact we actually are working with a manufacturer now who actually wanted an indication in congenital heart disease, so I'm afraid to talk about that more in case this doesn't happen, but this would be unique in our experience.

Other people have mentioned various advantages of networks, one of them is flexibility, so we have had one trial that just didn't go, it wasn't going to work, and it was fairly easy for us to shut that down, and then – because we had other things going on, we had other things in the queue so it's not as if you stood up a whole trial operation and then had to cancel it, we have other things to do. We are also busy training young investigators, we have formal career days, and involve young investigators in as many of our activities as possible. Danny is quite right, you need a benevolent dictatorship to run a network, and make sure people are doing what they're supposed to do, and we have that in our protocol chair and our leadership, and we do publish everything we do including our mistakes and lessons learned.

Anne Zajicek: Thank you very much. Betsy, please.

Betsy Peterson: Hi, I'm Betsy Peterson and I'm the Founder of the Children's Heart Foundation and I still sit on the national board. And I'm also the liaison for the Foundation to the different groups here in Washington to try and make sure that we have a pulse of – sit on the pulse of what's happening in terms of research for our patient population. And as Gail said, congenital heart disease is the most common birth defect that occurs but for the general public that's really not a known fact. And for a parent who has a child with a congenital heart disease that can be frustrating.

So one of the things that the Foundation is focused on is to fund congenital heart research when we started in 1996, that was 18 years ago, there wasn't an organization out there in the United States that's solely focused on congenital heart research funding. And that was a niche that we decided was important and the physicians we spoke to in the area felt it was important, so we work together with the physicians to start the organization. We've now funded 57 research grants, some of which have gone on to become NIH projects, and they vary from being clinical research projects to becoming focused on device issues, which is what we are here to talk about today, at least I am.

And as a parent I just want to talk from that perspective, it's difficult for a parent to consider having their child in a clinical trial with the device unless it's life-threatening indicator. And

several of the devices – well, actually mostly all of the devices that the pediatric congenital heart community have had to deal with are devices that are off label or hand-me-down devices from the adult community, and most parents don't understand that when their child is going to be facing surgery. They have no idea that stents and catheters are being used aren't specifically designed for children.

So that said, it's really important that communication be conducted to allow parents to understand that having your child in his study actually can benefit not only your child but also other children because new devices need to be generated for a specific population group, which is ours, which has actually been stable, it hasn't decreased or increased over time, the lifespan as long as they've been recording congenial heart disease. And now you have a patient population that's grown into adulthood. Our physicians have been able to get our children into adulthood, and you have a whole new set of a difficulties with devices that are allowing these children to grow into adulthood.

But I just want to say that it's really important that we continue to encourage studies that are focused on devices because without those a lot of these infants and children would never get to adulthood. So that's really where our focus is. I'm trying to make sure that more research happens in that area.

Anne Zajicek: Thank you so much. Let's shift now toward the efficacy areas. Could Katie Clapp say a few words please?

Katie Clapp: I'm Katie Clapp, and I am Cofounder of FRAXA Research Foundation and we fund research on Fragile X syndrome. We've been doing this since '94 when my two children were diagnosed with it. We went through the basic process of thinking of ourselves as a mini NIH. Back then we knew the gene, we knew the protein missing, so we started funding C grants to understand the cause, and then look for treatment targets. We took that through lots of animal studies, mice, flies, IPS cells.

And 10 years later, we had some really good exciting treatment targets. So then came the hard part, and so we funded a few clinical trials because very small ones, because there hadn't been any done in Fragile X. We knew we had outcome measure issues, recruitment issues, we knew we had and we've been working on that, and I would say that's where patient and parent advocacy groups really can be key because we parents all want to know somebody who's been through it, and have somebody to talk to when they consider trials.

The problem is that now we've had some really big trials funded by major PhRMA, and unfortunately the first couple of Fragile X trials have failed. Now for those who don't know, Fragile X is a single gene developmental disorder causes autism and intellectual impairment, but

it has a very simple cause. It's got this key so it's an exciting thing to study, and honestly we really thought we had it nailed.

Now why did the first trials fail? The first time a trial fails, we thought it was the drug; the second time a trial failed with a different drug, I personally now don't think it's the drugs, I think it's the trial design. So we have a lot of work to do to figure out outcome measures, to perhaps tweak the ones that are already in existence, but as a parent having gone through the trials myself, and having talked a lot to parents who have gone through. And then lots of parents whose kids are now taking the drugs because these are Phase 3 trials with continuation phases.

So there are kids and, well, adults really and adolescents out there with Fragile X, like my son who were on experimental new medications and everybody around them says, "My goodness, it's working." And yet the trial failed. So that's where we are. In this summer a whole set of people had a drug taken away, it was another child that failed and the continuation ended, the drug was removed, the parents were terribly upset, but what was remarkable was so were the clinic directors, the people who had to take the kids off the medicine, they saw a difference.

So I just want to say, I think we've managed to find some good drugs and get a good signal, we just can't measure it in a way that makes sense in clinical trials, that's our big priority now. Thank you.

Anne Zajicek: Thank you. Could we next hear from Jana Monaco from the Organic Acidemia Association, please?

Jana Monaco: Hi, thank you, good morning. Yes, I'm with the Organic Acidemia Association, and I entered that organization like many parents before me whose children were diagnosed in a coma on life support, because they were not screened at birth for their condition. So many have gone before me like that, and I also have another child who was screened as a result of the first one, so I have a normal child functioning with a disorder, Isovaleric Acidemia. And my son who is 16 has very complex health issues and intellectual and developmental disabilities as a result of his late diagnosis at age three and a half.

I represent many of our families on our organization who came into an organization like this because the fact is, the rare disease world is an intimidating world for families. They come in and feeling like they are the only one and they do want to connect and support. On the same breath we have many families who are involved, whose children, thanks to newborn screening expansion have been diagnosed early on and are thriving as normal little individuals, but the fact is they are growing up. And patient's families, what they want to see for their children are to grow up and experience a normal lifestyle, and grow into adulthood and experience health as best as possible.

The realization is screening has really been improved, we've celebrated that with the 50th anniversary recently, a follow-up in treatment is really critical and some of our conditions that Dr. Goldsmith mentioned there are lot of issues involved, it's not just the disorder. And truly researchers and clinicians don't fully understand the impact of everyday conditions in diseases or environmental aspects on individuals with these conditions. And that's where we really value and see the need for research and trials.

So organizations like ours are small numbers, however, we are international, and we are almost a self-contained database. We've overcome many of the barriers that researchers experience to that they had in order to achieve a trial and seek patients. So by utilizing advocacy groups, such as ours you can bypass a lot of those obstacles and really truly connect with those patients.

And when we are talking about small numbers, these numbers are really already in their own little groups. And so it's easy, and these families, these patients really do value the need for research, and they understand, especially those of us who have had very negative experiences, the need for research to understand these disorders over the lifespan and so we've supported not only for our own children but for others.

Some of our organizations such as ours, we do also have our own little funding resources because we do value it that much. We've realized that these conditions, everybody wants a cure, everybody wants improved therapies and so forth. For some of us that's enzyme replacement therapy, many of our children do have to go through transplants, and many families would like to see, maybe that step not having to be part of their child's life. And by using research trials, that's going to be an avenue to seek those possibilities. So I think advocacy groups really hold a key to true effective access to the patient population.

Anne Zajicek: Thank you so much. Could we hear from Cynthia Le Mons from the National Urea Cycle Disorders Foundation.

Cynthia Le Mons: Good morning and thank you, Anne, for the invitation and for the opportunity to participate in this exciting workshop. I think that there is a real need for the open discussion in the platform that's been created here. I want to add my voice to the other advocacy leaders in terms of the role of advocacy in developing clinical trials and driving research.

Our organization was started in 1989 by a handful of families that were affected by the disease and there was virtually no hope at all for survival. Over the years we've taken the lead in driving the research that has improved the knowledge of the condition and accelerated research for new therapeutics. And I wanted to give you an example of a successful collaboration that came from a network that we had the opportunity to partner with.

In 2003 NUCDF partnered with a fantastic group of committed researchers that were already re-established for urea cycle disorders, and clinical experts to answer an RFA that was put out by the Office of Rare Disease Research to establish a consortium to accelerate research for rare diseases in a preclinical care. It was called the Rare Disease Clinical Research Network and it is in existence now for 10 years and is extraordinarily successful.

The network is funded by ORDR in partnership with several NIH institutions to develop a collaborative model between clinical researchers and patient advocacy organizations to increase research and improve access to clinical care. So part of this model was also to train young investigators and clinicians to improve access across the country. For our disorder we had maybe two or three centers in the entire country that have the expertise to treat the disorder. So we obviously realized everyone can't get on a plane with a child that has a severe condition and travel to see an expert, we wanted to make sure that within their geographic area they could have access.

This support from NIH along with matching philanthropic funding resulted in a model consortium and we currently have 17 clinical and research centers in the US, Canada and Europe. We are also partnering with the UAE and Japan on to expand the network. The foundation of our consortium was the establishment of a longitudinal study for urea cycle disorders.

Now previously most of the research and knowledge of urea cycle disorders had been driven by anecdotal evidence, so this longitudinal study was set up with the and facilitated by a registry that informed and resulted in a number of pivotal studies work and clinical trials for UCD, including the approval of two orphan drug products and an ongoing development pipeline.

NUCDF fostered successful collaborations with industry to develop these clinical trials to address unmet needs in our community and develop drugs that met the FDA bar for substantial improvement. We had one orphan product that was developed in 1996 but the burden of administration was so heinous that some of the older children that had survived chose to not take their medication and died rather than live with the burden of this product.

So NUCDF decided that we would take a collaborative approach to overcoming barriers, problem-solving and communicating results during development process. We've partnered with a pharmaceutical company and we are in collaboration with them in all phases of the end stages of the trial from communicating the unmet needs to FDA and working with the regulatory officer, recommending clinical experts to ensure it has quality data came out of the trial, and that the trial was safely conducted because urea cycle disorders are very nuanced, have a very nuanced management. We wanted to make sure that only the expert investigators would be in charge of the clinical trials, both, again, to assure the quality of the data and to protect the safety of the participants.

We educated our families about the clinical trial and successfully enroll the trial with a waiting list, and inform the company about the nonmedical barriers to enrollment like geographic issues, thinks that Jana was mentioning about the condition which would restrict participation or traveling long distances. We were also involved in the advisory and investigator meetings, the interpretation of the local trial data, and consulted regarding the development of the NDA.

Our role is really over-achingly to make sure that the process was patient centric and that a culture of transparency enabled all the stakeholders to make fully informed decisions and utilize a collective approach to achieve the successful goal of approval. Ultimately our urea cycle disorders consortium in these collaborations resulted in improved survival rates, improved outcomes and have significantly lessen the burden of this condition on our families and patients. The research has increased about 400% in the last seven years and our hope has never been greater that we will find a cure for this disease.

For many years when we said that there was a cure, we got a lot of eye rolling, and I think that we have to have that as a goal if we can't talk about then we'll never achieve it. So that is one of the directions that we are moving in now with RNA investigations stem cell therapies, and enzyme replacement.

Anne Zajicek: Thank you so much. Could we hear next half from Robert Beall from the CF Foundation, please?

Robert Beall: Thank you, Anne. I appreciate this and it's nice to be here with this pediatric community, or I think maybe next year for the first time we will probably have more patients with cystic fibrosis over 18 years of age so CF would no longer be considered a pediatric disease. But for the time being we'd certainly welcome these opportunities.

In 1998 we came to a very significant crossroads in our Foundation. We've had the CF gene for about 10 years; we had a good working hypothesis. I became very frustrated with the fact that we were not getting the biotech and biopharmaceutical industry engaged in cystic fibrosis. So we said how are we going to entice them? How are we going to de-risk them to enter into the rare disease of cystic fibrosis? Because we do only have about 30,000 patients.

So we set up a de-risking model, some of that was financial, I'm not going to go into that today, but we have probably invested over $400 million since that period. With biopharmaceutical partners to bring – to create a very significant pipeline of about 30 drugs that are currently going to clinical trial development. Most significant of the products of that effort was Kalydeco that was approved in 2012, which it works for 4% of our patients as a disease modifying oral drug that came out of a collaboration we had with Aurora Biosciences, Vertex etc., and represents from us about $75 million commitment for that drug alone.

But more importantly than just the financial impact of our network and our therapeutics development program was the fact that we rapidly recognized that all companies needed access to the patients and access to data, data-driven, and that's also something that's very important for our relationship with the FDA. And that's what I'm going to stress because I really do think it's important to recognize.

One of the first things we did, fortunately for us from 1965 on our Foundation's, most of our patients have been seen in a network of care centers. These are care centers that are accredited and funded by the CF Foundation and care is based upon evidence-based guidelines. So but one of the things we had to do was to be able to formalize a clinical trial network using these centers. So currently we have about 50 employees, contract employees at Children's Hospital in Seattle, led by Dr. Bonnie Ramsey and we have a very significant team of individuals who have biostatisticians.

I think Nicole Hamlet – I don't think she was here yesterday. Nicole Hamlet was here yesterday talking about the biostatisticians, the data we collected, our ability to do sample collection, specimens, we can run Phase 1, Phase 2 clinical trials. We still let the companies run their own Phase 3 clinical trials, that's just too much for us to do it, but that has become a very important component. That's our coordinating center and we've taken our care center network and we've superimposed upon that. About 70 of those, 80 of those sites now are accredited where we actually have a research coordinator in those sites that are paid for by the CF Foundation to facilitate clinical trial recruitment, development and conduct in the CF Foundation.

So that's our clinical trial network and we could certainly go into more details but I convinced them already, 30 seconds over. The last thing I wanted to make sure that I emphasized is that you just can't have access to the patients without data, and the patient registry is something we haven't talked about a lot today, but I think it's probably – and when we talked to Janet Woodcock and about Kalydeco approval, she says, "We need a natural history of every disease." And we have had our patient registry in place since 1965, and every single patient's data, genotype; phenotype is in our outpatient registry, so we have a very good natural history of the disease.

As part of that process, we've also created a culture of research for all of our patients, our clinical trial recruitment is amazing, it's amazingly fast because our patients know that their data is going into the clinical trial process. It's going into our patient registry, and we've been able to create that culture in our community. So I think that certainly has attributed to the emphasis and into the momentum that we have in cystic fibrosis but I can never understate the importance of the patient registry because when we work with the FDA, when we talk about PROs, when we talk about outcomes, when we talk about biomarkers, we come with data, we don't always come with demands.

And I think that really has helped us in terms of trying to pave the way for our tech sector and our biopharmaceutical partners to have the collaborative discussions that we have had with the FDA over the years.

Anne Zajicek: Excellent, thank you so much. Could Ed Connor speak about the Clinical and Translational Science Award next?

Ed Connor: Sure, thanks, Anne. What I thought I'd do is primarily talk a little bit about product development in kids in general and a little bit about the Clinical and Translational Science Award program, but I've been doing product development in pediatrics for about the past three decades, and that gives you a certain perspective on the commonalities and issues that are addressed in both pediatric research as well as in rare and orphan disease research.

And I think that for most of us who had been in that space for awhile, when it started out back in the early HIV drug development days, the origins of patient engagement and advocacy in a way to bring forward regulatory change as well as clinical trials change for the purpose of really developing products and the kinds of interactions between academics, industry, governments and other, and patient foundations to actually deliver on the promise of delivering products, not just delivering information.

So it's really from that perspective that I'd like to make a few comments. I've been involved in that capacity in a variety of different ways originally as an academic running large networks of the Pediatric AIDS Clinical Trials Unit, and then ultimately in biotech for 15 years, developing pediatric products that are primarily drug and biologics based. And now back in academic medicine working with some of the networks that you've heard about as well as others in trying to advance product development.

And I think that there are a lot of, many of us who've worked in pediatric product development for quite some time come from the perspective of rare and orphan diseases. They are all subsets of rare and orphan diseases that we've been working to try to get approved. And whether they are traditional rare and orphan diseases or conceptual rare and orphan disease, the goal is to actually advance those to actually commercialization and ultimate availability to patients.

I think for a long time the commonality between pediatrics and rare and orphan diseases has come from the fact that that actually they had been neglected, I mean, for many years, it's been very difficult. We've recognized the gap that exists in the knowledge base about how to use drugs that are available for adults and children, particularly in young children and neonates and critically ill infants. And we've also from the perspective of rare and orphan diseases have been waiting for science to advance far enough to be able to provide candidate opportunities and products.

And I think that, well, that's there are a lot of commonalities in the challenges, there is also a substantial opportunity, that's the good news of what's happened over the past several decades. The good news is maybe not a perfect storm but it's at best a storm. The ability to now be in a position really to have legislative changes and regulatory changes that really drive pediatric data collection as well as scientific advances that allow candidate products for rare and orphan diseases to be pushed through the system and that provides us really with an opportunity to deliver on what we've been advocating for the last many decades. And that is filling the knowledge gap of pediatric drug development and advancing rare and orphan drug development.

And while that opportunity has many challenges associated with it, it also is a fundamental opportunity that we need to be able to take advantage of. As we've advocated for this need, we've now really have the opportunity to deliver on it, and the question whether we talk about that in the context of networks or we talk about that in context of stakeholders that are involved in the process, really that it's now time to actually deliver on what is a substantial challenge of collecting data that can actually move the needle when it comes to product development.

So I think that that creating these new products and moving them through the system comes with a significant responsibility, back to all the stakeholders that are involved in this process. And it also comes with a significant level of urgency, that is we – it has been great to talk about an advocate for these things but now the time is to actually move them into action, and doing that has created the opportunities and some significant challenges, but I think that the ways in which we go forward really revolve around a couple of important themes.

And the themes that we've heard talked about over the last few minutes, but maybe ones that we need to codify as both the principles that we used to go forward as well as the issues that we use to judge ourselves as to how much progress we are making. And to me when we think about networks as a place to do this, to do this work, there are some characteristics of those networks that have worked, that are really quite important.

And one of them is to recognize that the principles of development science of doing product development are quite different and distinct and unique compared to just doing clinical research. And the knowledge base in understanding and discipline of doing development science is something that we think we do much better than we actually do on a day-to-day level.

So understanding what it takes to get through regulatory approval, what it takes to have a goal oriented approach to clinical research where we actually look at what the endgame is and then design the project to get there, rather than iteratively moving from one knowledge base to another. Really sort of important stuff but that mindset and concepts are integrated into some networks that are very effective at moving projects forward, but not in others.

And frankly in this space of pediatric and orphan drug disease, people have mentioned that nobody can do it alone, it's all a partnership. So while industry may have experience in doing product development, that understanding needs to be relatively common among all the stakeholders, so that we can actively participate in a much better way collectively in how we go forward. So the principles of development science in any network that's effective needs to be focused on and understand that what the goal is at the end of the day and what it takes to get to regulatory approval and labeling and to operate under those principles.

The other principle is really the collection of regulatory quality data. At the end of the day the goal is to produce data that can be used for regulatory approval, and that's very different than data data. It requires a level of stringency and quality assurance that is quite a bit different, and the infrastructure to do that in an efficient way is different than the traditional clinical research infrastructure, and it involves a whole set of different kinds of skills from very strong leadership things that Danny was talking about in terms of driving the system to its goal, down to common harmonization of data elements and the ability to collect information in an efficient way.

So all of the issues that can be captured under this notion of delivering quality data is a characteristic of networks that work effectively as opposed to networks and create a lot of information, but not necessarily move the needle to the goal of moving products through the system. And I guess the last thing; the other principle that I think quite important is something that could be put under the aegis of engagement.

And engagement is really, partly the engagement that many of the family and patient groups have talked about, but it's also engagement among the various stakeholders in a safe harbor kind of way. Product development and these issues that one has to deal with, whether you are back 20 or 30 years ago in the early HIV development days are now are messy. They are complex things. And when you look at it on the surface, I think Marshall Summar a colleague of Children's yesterday called moving into the orphan drug disease space from the non-orphan drug disease space, like joining a family that's kind of loud and chaotic, and at the surface it's kind of complicated to try to figure out.

That's a good thing, and the reason it's a good thing is because particularly in drug development environments, we have to get it right at the beginning. We don't have the luxury of rummaging around in the data later on. So we have to get all of the engagement early, and the ways in which we work with each other, not just patient engagement with the medical system but also industry engagement with academics. We've created an environment in which very often it's more complex to get together and really hash out the issues because of concerns over problems as opposed to finding ways of actually making that happen, which ultimately advantage patients.

So to me the issue is that we need to focus on networks that are knowledgeable and increase the ability to get to issues related to development science. We need to focus on making sure that the

data that comes out of any system is regulatory quality data, and we need to find the platforms and facilitate the platforms that allow us to actually have that kind of engagement where there is a level of trust among the patient community, the academic community, industry etc., and the conversations can really be had, that need to be had at the beginning, so that we get it right before we deliver on the information. That's sort of the primary issue.

The CTSA effort at this was an example pilot project of a point person project, which was CTSAs have 60 some sites around the country, and the pediatric efforts of that, we are trying to engage these various dynamics in these conversations. So we identified people at each of the sites started to have industry and others come to us to get some advice. And frankly over a very short period of time, a variety of different levels that strategic advice to companies down to actual execution of protocols and putting groups of people together to do studies has been quite successful as a pilot in order to be able to facilitate these kind of things.

Anne Zajicek: Thank you very much. Steven Hirschfeld will speak on behalf of the EU initiatives.

Steven Hirschfield: Hi, thank you. First of all I also feel humbled hearing everybody's perspective in particular from patient advocates and parents, it's motivating. I was somewhat concerned that after everyone spoke there would be nothing left to say, but there is a little space still, and that is, what is the Eunice Kennedy Shriver National Institute of Child Health and Human Development doing in a project funded by the European Commission? And I'll try to explain that in 90 seconds or less.

So at the NICHD which is the faster way to say the name of our organization, we have had over the course of the last three decades, we have supported at any given year 50+ networks and everyone is devoted to a disease or a body part or something or another. And it's highly parochial they can't talk to each other they can't exchange data, they all have their own governance structure, and we have an enormous amount of not only redundancy but discord.

So European Commission funded efforts which we now play a role in, that started three years ago called Global Research in Pediatrics, and the theme here is harmonization of process. Can we get the data sets from various networks to talk to each other? Think of the power of that. Can we get the data of sufficient stringency and quality to pass muster for regulatory agencies around the world? Not just one government's policies or perspectives.

Can we get processes in place where we can harmonize the human subject protection oversight, which varies from region to region? And can we get the mechanics of collaboration to write protocol, so that some of the challenges and some of the very informative anecdotes which we heard over the course of this morning become history? And that we do have a collaborative and

not only cooperative, but predictive and manageable process to initiate, implement and then disseminate the data from clinical trials.

So the goal is that this Global Research in Pediatrics is indeed global. It covers Australia, Asia, Europe, and there is some participation through the World Health Organization from Africa and South America. We still haven't reached out to the penguins in Antarctica but that'll be the next phase. But in any case the idea is to get process harmonized so that we can reach the goals that everyone has been talking about.

And one of the challenges is that all the people who participate in clinical trials historically have different roles and different goals. And we need to ensure that the roles and the goals are understood and are again harmonized. Harmonization does not mean identical, it doesn't mean everybody does the same system, but it means that everything can talk to each other and that there is interchangeability of not only data but of concept and understanding, and we think the commitments are always there, but we need to bring those to bear on the process. Thank you.

Anne Zajicek: Thank you very much. My vote in the interest of time, Dianne, if you don't mind is that we turn our attention to our audience and see if we have questions and discussion points and then we'll move from there. Is that agreeable?

Dianne Murphy: Totally cool.

Anne Zajicek: Good.

Dianne Murphy: People, bring up your mic, some of you did, some of you didn't, but yesterday again the complaint was that the speakers would fade away, so when you're responding to the audience do bring your mic forward please..

Anne Zajicek: Okay, audience, participation, questions, comments. I have a general question, is anyone here from PhRMA? Okay, alright. So I work for the government so I don't know the answer to this question. So what has been the interaction between big PhRMA, small PhRMA, what have you and the advocacy groups? If anyone willing to take a shot at that or? Yes, please, oh please, yeah. Thank you.

And while she is coming up, I also would like someone to come up and talk about the impact of the EU legislation on the clinical trial designs and the impacts of the interacting with the network, so again I want someone from the audience to come up and address that from PhRMA. Thank you.

Christina Bucci-Rechtweg: So I'm Christina Bucci-Rechtweg, I'm with Novartis Pharmaceuticals, and there are many other PhRMA people in the audience, they just didn't raise their hand, but I know who they are. So in terms of the interaction, there is actually quite good

interaction amongst the companies through the trades typically. In the individual program work that we do, typically it's on to one-to-one basis with the advocacy networks that are out there. So for example if we are doing work in the Fragile X space, and you gave a very eloquent presentation. We might be working directly on a company basis with advocacy groups.

I have not seen so much when there might be multiple competitors in the same space, that there is work unless there is a shared public-private partnership related to a biomarker development or related to an epidemiologic data collection, that's taken place in a coordinated approach, but as it relates to product development, it's typically in a one-to-one relationship.

Anne Zajicek: Now does this typically have to do with patient enrollment or clinical endpoints?

Christina Bucci-Rechtweg: Mostly on the endpoints, enrollment has been a problem I think regardless of whether there is academic research going on or industry research. And I think both Ed and Daniel really did a nice job of highlighting ways that we can improve. And I actually wanted to come to that a little bit about the network discussion because one of my colleagues whispered very well in my ear, everyone's definition of network is different. Just listening to the table in on the room, everyone's definition of network is different.

And I think one of the ways that we could enhance the space that we are working in as it relates to pediatric drug development, which is almost entirely within the orphan disease space is to really come to an understanding of what network means. And to say there are different classes of networks, and they all serve very important purposes. But in what aspect do we utilize those different networks or advocacy groups for collaboration to get better outcomes?

Anne Zajicek: Thank you very much. Yes.

Lawrence Charnas: Lawrence Charnas from Shire. We have a rare disease business unit and have developed expertise in natural history studies, so our engagement with patient community begins at the inception of a product. There is no point in going forward with developing a new molecular entity if you actually can't get it over the finish line as Ed pointed out. And I think those relationships can be individual if we're the only company in a space or if it's a competitive space, such as Duchenne muscular dystrophy. We figured out ways with other industry partners and the Patient Advocacy Groups to work together because ultimately it's all about the patient, we need to keep our eye on the ball.

Anne Zajicek: Thank you.

Charlie Richards: Hi, I am Charlie Richard, I work for Oxyrane, I previously was at Shire, human genetic therapies, and you'd asked what kind interactions we have at both companies? That always begins as Larry said from the very earliest step, so some of the things that we've done, our work with the patient support organizations to provide travel for clinical programs

we'd actually contracted previously with a more traditional travel group but they didn't really understand the travel needs of them and the parents.

So this a moneymaking operation for the patient support organizations, but most importantly it was getting the patients in the right situation in the hospital for overnight stays. We've worked with the organizations to provide us with an idea of, obviously of how many patients in rare genetic diseases that are in their databases over 20 years and sort of what kind of diagnosis they have. And one country, particularly we were doing a study and a natural history disease, and this country organization has a national ethics committee and they said, this doesn't provide any direct benefit to patients because obese cerebrospinal fluid taken with anesthesia with these patients.

And we got nowhere with talking with them, and finally the patient support organization stepped in and said, "Look, this is a preamble to a clinical trial. We are going to go in front of the regulatory board and argue the case and that really worked out well. And so we are able to get a natural history study started in a country from an ethics point then otherwise we wouldn't do that.

So there are many other ways, I mean I can't imagine. The patient support organizations are always hungry for information, and so we have regular dialogues to provide as part of the newsletters to get out where we are in the trials, and I think that's probably for motivated parents one of the best distributions for notifications of trials of anything we can do better than clinicaltrials.gov, it's a patient support organization newsletters. Thank you.

Jayne Gershkowitz: Good morning, I'm Jayne Gershkowitz, Head of Patient and Professional Efficacy at Amicus Therapeutics and very similar to my colleagues Larry and Charlie who we all know each other pretty well. We also work in the rare disease space, particularly in lysosomal storage disorders. And all I want to add is that, what we do with the patient organizations and individual patients is it's really a relationship building effort that starts at the very beginning, prior to even having clinical trials available.

And one of the things that we do in a longitudinal way is that we have a patient advisory boards. So, just as we have our medical and scientific advisory boards, we see patient advisory board function being equally as important. And this way we have ongoing reason to look to the patient community to ask for input, not only around potential protocol design but you really understand what the unmet needs are in the community to understand issues about access and reimbursement, and things that affect us cross functionally so that we can do a better job in all areas, and we have found this to be very successful.

And then when there is a study going on, of course, with the ongoing communications that we have with the leaders of the patient organizations, we can have focused work but we also have things going in an ongoing basis, and we found that to be very effective.

Anne Zajicek: Could I ask you an associated question?

Jayne Gershkowitz: Sure.

Anne Zajicek: Sorry. One of the questions for this group is what makes a good network, what could be better? So do you have any comments in that area also? So I guess the question is, so is pharma making the determination who the clinical sites are or is it clear from the advocacy groups who the clinical sites would be or how do you determine which clinical sites are using and how do you decide whether they are doing good job, not a good job aside from, I guess the recruitment would be the most obvious point?

Jayne Gershkowitz: I agree with your comment that network and the definition of network can be different for everyone, but to your question specifically, patient advocacy has been part of clinical site assessment because of the information we have from the patient organizations internationally knowing that they come and say, hey we have an interest in your study. We have patients who cannot get onto a current standard of care and they are interested in investigational product.

And it could be that we have a disconnect between the information that we are getting from the patient community with what may be coming from the physician community. They may be saying, we don't have patients interested or I don't have people available for your study, and then we have – the patient organizations will actually go to the treatment center, so go to physicians and to study coordinators and say, "We have people who are interested, will you bring this study to our community or our region or our country?"

And that's when the rubber meets the road, and we actually, I can say that in Australia we had a significant difference of opinion between what physicians were telling us awhile back and what the patient organization was telling us. And then the patient organization went to the nurses genetic counselors and they said, "No, we are interested." And that actually ended up being one of our highest enrollers for a study. So we work it from very different angles, and I would say it is a network and the network shifts and changes depending upon the information you have and the needs.

Ciara Kennedy: Thank you. Ciara Kennedy from Lumena Pharmaceuticals. We are doing research in rare liver diseases for both pediatrics and adults. I would say one of our best relationships and one of the most productive relationships we've had is with the Alagille Syndrome Alliance with Patient Advocacy Group. And we've working with them since day one

in terms of developing a novel endpoint, clinical endpoint to patient report and outcome endpoint.

We've attended their patient information days to conduct interviews and it's been the two of us marching down the road together to come up with an instrument to measure our symptom that's of critical importance to the patient. And that group also sits on the, they have a seat in patient's advocacy for the children network, which is the Childhood Liver Disease Research and Education Network. So they also are a voice for our interest in terms of pursuing studies, clinical studies and Alagille syndrome within the network.

And the network obviously has many priorities and many different diseases, so they convey to the network the importance from their perspective of pursuing studies with us. So again we've heard today it comes from multiple angles. So I'd say that that's been true in our experience as well. But it's been, just such a great relationship in terms of defining from a patient or the parent perspective, what's important, how it impacts them and how you measure it? And then they have been a great conduit for us to access patients and parents.

Dianne Murphy: I think one of the things we also need to address here, because we are hearing that we have to, and it's very important, and we talked about this yesterday, is what is important to a patient as an endpoint, what is important to the researcher, and what is going to be accepted at FDA. Because we are lacking pediatric endpoints in many areas, and if we had time or maybe we use it to prepare the summary, I would ask Lynne Yao or Greg Reaman to talk about some of the issues with getting actual validation during trials. And Ed, you and I've lived through this with HIV,. I mean this is a big deal.

So you have to have those kinds of agreements upfront and all the groups have to know that. So again, I don't want to interrupt the discussion but I'd like to hear some more discussion on that too and how to facilitate doing that. Thank you.

Jeff Siegel: Good morning, I'm Jeff Siegel, I'm with Genentech, I don't have that much to add to what my other colleagues from industry have said but we look very much to Patient Advocacy Groups for a number of things, for our clinical trials. One is to increase awareness about our clinical trial among patients to help recruit our trials. And the other is to provide patients to give us feedback on our protocols to make sure that they are patient friendly.

With respect to endpoints that Dianne was mentioning, I can just mention that we have a study ongoing in ANCA-Associated Vasculitis in children. And fortunately academics in that field had developed a prototype of a vasculitis index that we could apply in the trial, and hopefully we'll be able to use the data to validate it.

Anne Zajicek: Thank you.

Mark Roche: Mark Roche from Lozane Consulting. We talked yesterday a lot about, yesterday morning about natural history data. And how important natural history data was, and Bob mentioned it today. During my time at Vertex, involvement, development of Kalydeco, the natural history data was critically important, that we knew the disease progression and we knew early on in very short studies whether we could have an impact on it and then help reduce the financial risk, the development risk that we are taking.

In my current role, I work with a lot of clients who are doing rare disease development, where there isn't natural history data. We talked yesterday about the expense of collecting natural history data. So I'd just – but we didn't come up with any solutions about who is responsible for it. So I think the Patient Advocacy Groups can be really beneficial there, so that when clients, and especially we were with lot of small clients, five people companies, these kind of virtual things.

They don't have the resources to collect the data themselves that Patient Advocacy Groups can be really important in collecting natural history data, so that these companies when they develop the drugs that we are not waiting for natural history data to do the drug evolvement because the patients are waiting, and we don't want to wait 20 years from natural history data before we can try and get a drug developed and improved. Bob looks like he want to –

Robert Beall: So I think that's a really good point, and fortunately we've been at of position. We've been able to start our patient registry many, many years ago, but I really do think and I think Ed touched upon this a little bit. I think it's critically important for us to start to take advantage of the CTSA network and the dollars that they have in the hope that they can start to create some sort of a framework for the smaller diseases to start to think about collecting some data.

This is an amazing resource and a number of access to patients and rare diseases in patients with rare diseases around this country that I would really hope that we can get Chris Austin and the group there to really think about this. And I know there is some efforts in that direction and I'm fortunate enough to be on the board. But I think that's critically important analysis, the CTSA's I think ought to think about how they can start to perform some of the infrastructure for some of the clinical trials in the rare diseases, because I think we do have to have that uniformity and so forth and the institutes need to get behind it.

So because everywhere there are all the major medical centers in this country have access to those patients, and there are some of them with the rare diseases are just going untouched at this point where I think the data could be very useful to the things that you need as that natural history is critical.

Anne Zajicek: I'll just interrupt for a second. Steven, you may be going to say this but NICHD has also been responsible for a fair number of observational longitudinal studies of patients as well.

Steven Hirschfeld: And I'll just add to that, you are right. But we also have a, I think fairly decent size, 100,000 plus family National Children's Study which will capture national history. There will be people with rare diseases, and almost every disease is a rare disease in child health. Through that study, and we invite partnership so if anyone is interested in trying to leverage that platform, and we could expand and adjust to accommodate various kinds of data collection. It's not interventional but it will be a 21 year natural history study and we would welcome collaboration there.

Anne Zajicek: You have about 30 seconds if you want to go ahead.

Ed Connor: Sure, I was going to comment on what Bob was saying. And I think that in general there are two elements to this. One of the things that are common to clinical trials across whatever the therapeutic area is, and that common infrastructure and knowledge base should be fostered and developed and it's going to take all the stakeholders to do that, certainly the CTSA is interested in that, but I think there has been a traditional partnership.

There is a very close working relationship between NICHD and the CTSAs between various places where in pediatrics we've often had to put together resources to accomplish common goal. So we do need to use the resources that are available to get these high priority things actually really done. And there is a lot of effort of working together to be able to do that.

Anne Zajicek: Good. It is 5 until 10, you've been waiting so why don't go ahead and speak.

Alejandro Dorenbaum: Yeah. Alex mine is both networks and the endpoints, so I cross paths with Ed in the Pediatric AIDS Clinical Trial network and I think that what made it possible for us to work was the push we had from advocacy to get therapies out to the children. If [ACTOP] in HIV had not been there, we would have been ten times slower than we were. A handicap that we have in networks is that they tend to be national or regional. And Ed will remember that we had a hell of a difficult time merging our network with a [penta] group in Europe to get pediatric trials done.

In pediatrics, we are not going to be able to do these in a single country. We will have to go international for these very rare diseases, and the network should incorporate in their charters the obligation and the capacity to work internationally, not only regionally or nationally. We struggle a lot with networks being very country or regionally centric. So that's my comment on networks.

On endpoints, we are struggling a lot with endpoints and pediatrics with a patient reported outcomes. And this is because children cannot report on a symptom, and we usually end up having to add a layer of trying to develop a PRO that is difficult to develop to begin with, with an observer reported outcome, because now it's the parent reporting on the child's pain or the child's itch or the child's symptom that is at play here, and that makes this process extremely complex.

Now, the saving grace in this disease is that the PRO group at the FDA is remarkable and I urge everyone that is developing a PRO to work with them very closely.

Dianne Murphy: We have three minutes and at that point we'll be at ten o'clock, so here is my proposal. We will use those last three minutes and we'll move everything ten minutes ahead, we are going to cut your break by five minutes. So we are going to go for the next three minutes, then we are going to take a ten minute break and then we'll start from there. So if the last two people would like to say something quickly.

Will Tree: I am Will Tree from Janssen. I'd like to pick-up on the gentleman from the CF Foundation's point, we'd been hearing a lot about Patient Advocacy Groups, very, very important input we've been hearing from Danny about benign dictatorships and how to run a network, but I really think what we need to understand because of the exigencies of the economics of pediatric care at major medical centers in this country, I'm speaking primarily about this country. And these are the centers that perhaps have the expertise and capability to do studies in rare diseases that the patients for whom might be drawn to these medical centers.

We need to pick up, I think on the CF Foundation's model and understand that we need to support those centers. We need to place people for our networks who will coordinate the networks at the centers themselves on site. It's not enough to have a great central management group somewhere in the ether or on the internet. I think you need people at the sites to actually coordinate these studies to actually advocate for these studies, to actually pick-up on Ed's point about data collection and the uniformity of data collection, and Steve's points, site actually investing in the clinical infrastructure at the sites is the way to get this kind of coordination that we are talking about.

Anne Zajicek: One minute.

Laurie Sands:I'm quick. I'm Laurie Sands with Hannah's Hope Fund. I feel it's very important that we all really stop referring to registries as natural history studies. They are quite distinct entities. We have contact registries, we have clinical registries, which contained phenotype, genotype information, much like Bob spoke about, the CF Foundation's clinical registries, where natural history studies are actually IRB approved studies where you bring in patients at routine intervals and do very robust functional assessments hopefully against validated scales if you

have them that are relevant to your disease like the Six-Minute Walk, therefore just the scale, you do MRIs to look for inflammation, you do nerve connection velocity test. Anything quantifiable that may apply to your disease that maybe a valid endpoint for a pivotal trial. So I think they are very distinct, unique things and I think we need to refer to them as such. Thank you.

Anne Zajiek: Thank you.

Robert Beall: Can I comment real quick because I think maybe we are referring to because ours is based upon four – our patients come in on average four times a year, and every encounter in terms of pulmonary function and all those parameters that was just spoken about are incorporated into the data so it does create from day one to the time through their continuing care, a natural history of the disease.

Dianne Murphy: I want to thank everybody. The discussion has been great. We will try to summarize this at the end of the day. We look forward to the next discussion which is going to, I'm sure, be at least as interesting, so thank you. See you in ten minutes, ten after ten.

Session Seven
Tolerating Risk and Uncertainty in Pediatric Clinical Trials

Skip Nelson: You will all notice that we did a little bit of reorganization. The room was not set up the way that I wanted it set up, so I just arbitrarily said let's change it. Space is important. The intent of this session is to have a conversation, and as I described it to the people on my panel, it's a focus group followed by Oprah or Oprah. I'm Oprah.

I'm Skip Nelson. I work at the FDA. I'm the Deputy Director of the Office of Pediatric Therapeutics. My area is Pediatric Ethics. The session that we're going to be doing today … Let me ask. We do have some of the handouts. Did everybody get a handout of the themes of the different sessions today? I don't intend to read through what you see for Session 7, but I would suggest while we're talking, because all of the panelists saw that in advance and they've had an opportunity to think about what we're going to be talking about. So, you could be reading that and looking at those themes. It's a page plus a little bit.

Basically the topic that we're going to be exploring is the judgment, the assessment, the decision, the point in time at which you, and when I say you I mean all of us, all of the various stakeholders, whether a parent, patient, patient advocate, industry, investigator, regulator, when you think you've got enough data to go ahead for that first child study. As part of that decision there are three components.

One is, what is it that you hope to achieve? What's the benefit that you hope to achieve? What are the harms that you're willing to risk in order to try to achieve that? The harm and the probability, there's both the harm that you're willing to risk and then the probability that that may or may not happen. Then, how much uncertainty about those two issues are you willing to tolerate when you decide to move forward? That's the judgment that we're going to talk about.

Then as you read through that page, you'll see at least my reflections on why that judgment is important in terms of the application of both the ethics of pediatric clinical trials, but also decisions to be made about proceeding. Do we have enough to move forward? I don't plan to say much more about that. My role here is to moderate and to engage our various panelists.

I'm also not going to introduce everyone at the beginning. But I'm going to ask, when you first say something, to just say your name and to give a little bit about yourself and your perspective, because the people here may or may not know who you are. They can't see the nametags. I will say, for the benefit of our transcriptionist, she does like to have a name before you say something because then they can notice that quite well.

What I'm going to start with, I've told the various members of our panel, thank you all for being here. I've said hello to some of you beforehand, but others I didn't have the opportunity. We just

got going here. What I'd like to do is start thinking about what is the benefit that we hope to achieve? Because clearly, as we begin to think about risks and we begin to think about the amount of uncertainty we're willing to tolerate, it's all I think framed by what that goal might be. So what is it that we hope to achieve? I told Andrew, Mark, and Holly that I'd start with them.

My own view is, what we're hoping to achieve, the benefit we're hoping to achieve really ought to be framed by the perspective of those that are in fact engaged with those communities that we hope to have an impact on. I don't have a particular order. I don't know, Mark, Andrew, or Holly, which one ... All right, we have 2 mics. We'll have one to hand around.

Mark Papier: Good morning. My name is Mark Papier. I'm the parent of a child with a rare and fatal disease, Niemann-Pick Type C. Currently Dillon is enrolled in a trial with Dr. Denny Porter at NIH and our goal is hopefully to delay the progression of the symptoms of the disease. There is no cure. When we received the diagnosis, which is devastating as you can imagine, we had no drugs. We had no options. We were desperate. When we were told that NIH is doing this clinical trial, our goal and our hope is that our son will have 4, 5, 6, 7 years of normalcy and that he'll be relatively symptom free because of these new drugs that are of course experimental.

Skip Nelson: Mark, before we go to Holly let me ask, when you say relatively symptom free, what are those symptoms that you thought were most important to you to preserve?

Mark Papier: The disease it's neurological. It affects his ability to walk, talk, swallow, and it affects his gait. Eventually it's almost like a childhood Alzheimer's. I know they don't like to hear that in the Niemann-Pick community, but there's no rhyme or reason when the symptoms occur. Different kids with the disease have various symptoms at different ages. Right now our son, he falls a lot. He has an unsteady gait. He has leg braces. Right now he is still able to go to school. He is still able to eat normally. He has difficulty with speech. He doesn't have seizures yet. Phil is going to talk about that probably later on. We hope to delay those symptoms so that he has some degree of normalcy for the next couple of years. That is our goal.

Skip Nelson: He is 11.

Mark Papier: He is 11 right now, yep.

Skip Nelson: Holly, do you want to come next?

Holly Peay: Thank you. I am Holly Peay from Parent Project Muscular Dystrophy, which is an organization advocating for Duchenne and Becker muscular dystrophy. Duchenne and Becker muscular dystrophy are neuromuscular disorders that cause progressive weakness. There are no approved therapies. A little bit about the benefits that parents are looking for. We've actually been engaged in a study funded by NINDS to look at people's expectations and experiences in clinical trials. What we found is first of all that this is a moving target. Families adapt over time.

As they adapt, what is normal changes. What we're seeing from families is that mainly what people are interested in is some level of stabilization. They would love benefit in terms of increased function, but stabilization is very important, keeping people where they are, with the skills they've adapted to. Also that they're focused on quality of life.

One of the interesting things we're finding at our study is that there is some disconnect with how patients and families define and value benefit versus how clinicians and sponsors in clinical trials value benefit. A little bit of difference in how that's defined and valued.

One of the other things I think that's interesting that we're noticing is that as our community gets more experienced in the clinical trial world, their expectations and hopes are changing. A pilot study that we did several years ago looking at one particular clinical trial, there was a lot of discussion about hope for a cure. And our community there is still some of that discussion, but in fact the hopes for a treatment through a clinical trial have actually been modified somewhat so that families now say hoping for a cure is naïve in terms of what could be expected from the things in the clinical trial pod right now. There's a lot of learning in the community and adaptation in the community, as well as adaptation to changes in children's function over time.

Skip Nelson: Thank you. Phil

Phil Marella: Yes, my name is Phil Marella. I have a son, Andrew that has Niemann-Pick Type C. He's actually at the NIH today getting his second treatment with cyclodextrin. He is a part of that drug trial. At the age of 14 he is relatively symptom free. Except that unfortunately, this summer he had an older sister who was just shy of turning 20 who passed away Niemann-Pick Type C. Dana was severely handicapped. She was in a wheel chair, she had a feeding tube and a tracheotomy. Couldn't walk, couldn't talk, basically required total care. But she was an important part of our family and important part of our effort. We have a foundation called Dana's Angels Research Trust. We work with researchers raising money with the Papier family and others pushing the research to really we hope to save these children.

I think the perspective that we look at it from is that we are going to find a cure. We're going to be able to save ideally the children we have now, certainly children in the future that are diagnosed with Niemann-Pick Type C. Where things like cyclodextrin come into play and where they're so critical is because they do buy us some extra time. We have one medicine that doesn't have FDA approval yet, called Zavesca. Many of the children are on it. Not all of them because it's extremely expensive. But we do believe that Andrew has benefited from it, it has slowed the progression of the disease. We hope to see that cyclodextrin is going to add benefit to that and slow the progression even further.

Then we're hoping to have really a drug cocktail that will resemble something like a cure, something that will arrest the progression of the disease or slow it down significantly. That will

give us time to get to what would be more of a cure. I think that's one of the perspectives you have to keep in mind for parents, is that we'd love to have that pill tomorrow that just takes care of everything, and makes your child normal. Ideally you want to stop the progression. But then you obviously you want to try to heal the child.

I think medicines can be found that will slow the progression of the disease. If you can slow the progression of the disease, it gives you more time to get to a cure. I think that that's what we're hoping with the research that we have going.

Skip Nelson: Thank you Phil. What I heard in common among the three of you is this theme of slowing progression. In turning to the investigator and sponsor community, I don't have a particular order with it, which anyone of the 4 of you represent that community want to respond. How do you begin to think about that? How do you begin to design your activities around that? There have been products that have been approved by slowing progression for survival endpoints where there is a fairly dramatic response, but some of these responses could be fairly subtle. How do you begin to think about that? How do you try to design trials that respond to these concerns in a way that's meaningful but also produces data that could ideally be reproducible? Again, a quick introduction before you get started.

Denny Porter: My name is Denny Porter, and I'm investigator in the National Institute of Child Health at the NIH. I've been studying Niemann-Pick disease Type C for about the last 6 or 7 years. This is a very rare disease. We were having a discussion earlier. There's rare diseases and then there's rare diseases. A few hundred patients, we don't have the luxury of 10,000 patients which is still a rare disease. You not only have the issue of being a rare disease, but you have a great deal of phenotypic heterogeneity, each patient is different. Low numbers and a lot of variability from a clinical trial standpoint make statistics very difficult.

Actually our goal as a researcher, our goal is to get the data that can establish that what we're doing, that the experiment that we did actually worked. Slow progression, we would consider stabilization or a minor, we want a go, but we would consider something that slowed the disease process as a win. But that means you have a very small effect size. Again, it comes back to this difficulty of statistics. Potentially small effect size, heterogeneity, variability and low numbers. None of those make developing clinical trials easy.

We have to work with the parents. We have to work with the family groups and the support organizations. I think our approach was initially a realization that we had a problem when we got into this 6 years ago. We said we need to step back and do a natural history study. Both the kids represented here participated in the natural history study, a study where they're not going to receive a direct benefit. But neurological disease, we have to be willing to do things that are uncomfortable or entail some risks. It's a neurological disease. We're happy to find a marker in

the blood. But you have to get it's a brain disease. Thus we do entail the risk in a natural history study of sedation and getting CSF for markers.

I think in trial design and moving forward, is putting that foundation in place. Not only the foundation of basic science of understanding what the disease is so that you can make good guesses, but then put the foundation of trying to understand the clinical disease that you have, and then try to leverage that into designing a clinical trial.

Skip Nelson: Who would like to? Dan and then we'll … In formulating your response, could you also comment on some of the problems about trying to do objective measurements of these outcomes versus reported outcomes. Think of when you have an exceedingly small population, the difficulty of developing those kinds of tools.

Daniel Ory: I'm going to continue a little bit on what Denny had brought up. I am Dan Ory, I'm an investigator at Washington University. I've been involved with Niemann-Pick C disease as an investigator for about 16-17 years. For the last 10 years I guess have been closely involved with the families and with the NPC community efforts, the advocacy groups. Probably for the last 6 or 7 I've really been working very hard in terms of translating therapeutics, or promising therapeutics from the bench eventually into the clinics. I've worked closely with Denny in developing the current cyclodextrin trial.

I want to bring up an issue related to this development which really has to do with what Denny had mentioned about the limited number of patients. This really factors heavily in terms of design issues in terms of how we are going to have to consider what type of endpoints that you can use, the role of biomarkers as surrogate endpoints, in trying to determine how you can get enough trial eligible patients to be able to be enrolled in these trials.

One of the issues that we have is that in NPC we're actually looking at a lot of drugs that are what I would consider repurposed. They're not new chemical entities. In fact, of the 4 drugs that I can think between the US and EU that are in development at this point, only one is a new chemical entity. The others are all basically ones that we have human experience with, or perhaps have already been approved as a therapeutic for another disease.

One of the problems that we actually have getting back to the numbers is being able to think about priorities. In fact with the NPC community, we have so few patients really to draw upon for the trials that we cannot simply open up let's say clinical testing on all of these compounds at the same time. We certainly could not support I think 2 pivotal trials at the same time. It just couldn't happen.

It raises very interesting issues for us in terms of how we think about prioritizing this. There are obviously competing interests with regard to the drug development. Some of us are more

academic based. Denny and I have been working closely with NICHD but also NIH trend in order to develop cyclodextrin and take it through its development. But there are other efforts that are underway that are more commercial based. Really the question is, what are some of the litmus tests that have to be met before the community feels that it's ready to actually take on a drug?

Part of this is risk and risk assessment, but I think there's also the issue of how much efficacy has to be shown in cell-based or anal based models, preclinical models before you'll actually be willing to take it on for a clinical testing? The reason why this is important is because if you do not prioritize and you have let's say drugs that you feel are clearly have a more promising profile based upon the preclinical work, if you don't basically prioritize, what'll end up happening is you'll end up not being able to sufficiently recruit or gather enough patients to be able to really bring that through to drug approval.

What this really comes back to is now to Mark and to Phil is the role of the patients' community working with the investigators to really decide how to work together in terms of deciding which efforts should be moved first, which ones should be moved ahead. It's a question that I think goes beyond just simply working with a few parents, but it has to do working with the national organizations, with the international alliances that we have. These are major issues that we have to deal with in addition to the real intricacies of the trial design.

Skip Nelson: Phil or Mark, any response to that before we go to Alex? I'll go to Phil and then Alex, you're after him.

Phil Marella: Phil Marella. I think that part of what Dan is talking about and even what Denny was describing, we have a very close working relationship with the researchers as parent organizations. There is the National Niemann-Pick Disease Foundation and the Ara Parseghian Medical Research Foundation. Mark's family has a foundation here and locally we have one up in Connecticut. There's others, but we work very closely together, getting together at Notre Dame annually. A lot of the parent advocates come, the different family foundations, the Parseghian Foundation puts that together.

We have an awful lot of collaborative effort that's taking place. There are certain labs that are a little more independent than others, but there really is a collaborative feel to what we're trying to do. I think that is a big part of why we've had the success that we've had. When you have a disease this rare, when you have a disease that is fatal, that is progressing every day although differently in each child. Again, as I said, my son Andrew has very few symptoms, but after his sister passed away he started having seizures. We had trouble controlling his seizures. His regular day is quite normal but for the fact that we have to worry about when he's going to have a seizure.

Every child is a little different. We have this close working relationship. I that that's made a big difference in the progress. The parents and the advocacy groups, the research funders and the researchers working together very closely.

Skip Nelson: Alex?

Alex Dorenbaum: This is Alex Dorenbaum. I worked at the beginning of my career in pediatric HIV in an academic setting. I transitioned then to industry and I see patients every week in clinic as well. I don't think that my principles of work in terms of research and treatment have changed from the day I started seeing children until today. We of course want to prevent disease first if we can. We want to cure it if we can. If we can't cure it, we want to prolong meaningful life as much as we can. If we can do that, we want to prevent suffering. For me that's the hierarchy of work that I have pursued in my life. I think the problem is that sometimes going for a cure may be too difficult or we may not have the technology to do that.

Take for example the inborn errors of metabolism. I was involved in the NPS6 program. We have an enzyme replacement therapy, but what we really want for those children is a cure. Probably cure would come in some form of gene therapy, yet gene therapy is probably very … we don't have the science yet to support the safe administration of a wholesale gene therapy for these diseases.

So the question is, how much risk are we willing to accept now to treat with an imperfect treatment in order to try to advance the science? I think the problem in pediatrics is that the guidelines and regulations related to pediatric research really vary from country to country and from state to state. The ethical decisions on which products can be moved forward are even more regional, sometimes from hospital to hospital about which products can be approved through an institutional review board. These variations do cause problems in research.

But the principles of research in general are the same. You want to respect people. You want to respect the person. You want to have an expectation of possible benefit for the person that is participating in the research. You want to have justice and equality in the opportunity to benefit from treatments. Those are three principles that have been outlined internationally for research in humans. These principles are reflected in the requirement of obtaining informed consent. That's what helps respect the individual, to minimize harm by preventing very toxic therapies to move forward. Also the concept of not neglecting populations such as children is a very important concept that I think I want all of us to embrace a little bit more strongly.

In my mind the vulnerability of children and their inability to provide informed consent raises particular ethical issues. Yet, the rules remain the same for research. I think we should be applying exactly the same rules we apply to adults to children. That is we need to respect the children with an appropriate informed consent process. We need to have a clear expectation that

the child may benefit from treatment. We need to have quality in the administration of research so that children can benefit from new therapies.

I make no apologies. I think we need to do research with children and I think we need to do it in a responsible manner. I worry a lot about you are in a stage now that it's a little different than the disease I was involved with phenylketonuria. Phenylketonuria was a disease where children who are missing an enzyme cannot process phenylalanine. They accumulate this phenylalanine and it's toxic to the brain, it causes mental retardation. Half of the children in asylums in the early 20s, 30s and 40s of the last century were peculiar patients. That was the main cause of mental retardation in the world.

Then someone figured out that if you actually give the children a diet without phenylalanine, you can prevent this mental retardation. This was devised probably around the 40s, 50s. Then, from the 50s on people worked on perfecting the PKU diet, the diet without phenylalanine. Let me tell you. I've tried it. It's horrible. It's really almost impossible to follow that diet. Similar to what we heard today from a mother here with their child.

The bottom line is for many years physicians were very content with trying to perfect the diet and improve the outcome of children without mental retardation. They didn't have as a goal to cure this disease. For that reason for about 20 or 30 years we did almost no research in PKU whatsoever to try to find a cure. What I can say is if there's anything that you need to be doing, is pissing us off, pushing, making pressure, making him sweat bullets until he figures out a way to solve the problem. Nothing short of that is okay, in my opinion. Nothing short of that approach is appropriate. I think we need to push for prevention and cure. Then, if we can't do that, in the meantime we can do the other things.

Phil Marella: We've heard Nick complain before.

Skip Nelson: That's all right. Holly, a quick response and then I'll go.

Holly Peay: Just a very quick response. I totally agree with you. I think the Duchenne community completely agrees that a cure is the goal. But I also think we need to be careful in the context of any one clinical trial that people have reasonable expectations. We understand that parents are driven by optimism and hope, which is very good and good adapt to coping. However, if we push, push, push for a cure and the research community uptakes that push, push, push for cure, that's what the discussion becomes. I think we just need to be careful that people go into a trial with reasonable expectations, understanding that parents already have very heightened expectations.

Skip Nelson: Larry, your thoughts?

Lawrence Charnas: Lawrence Charnas, I'm in the Discovery Medicine at Shire. I'm trained in adult neurology, child neurology, and medical genetics. My wife once said that I never met a training program I couldn't enjoy. She did enjoy it, and that's another story.

I have several thoughts. The first is, I hope Leo Tolstoy forgives me, as I paraphrase, common pediatric diseases are common, every rare pediatric disease is rare in its own way. I think we've have heard about lots of difficulties in rare diseases. There's similarities, but the uniqueness create specific challenges.

When you really want to think about a clinical benefit in a clinical trial, the risk has to be weighed against the time in which a disease is going to progress. Is the patient or the family at a stage in a medical addressable and the risk of going in with a novel molecular entity that's never been in humans before in an individual with the promise of benefit? If you have an animal model, where it looks very good, and the disease is rapidly progressive, it may be worthwhile. If you think you know what a change looks like. If the uncertainty of the disease progression is low so that you know what it's going to look like, you know if you had benefit and you know what doing nothing looks like, then it's worth the risk. The flipside is, if you're going to measure a biomarker you'd have a very high bar.

The specific risks I think have to be considered on an individual basis, by whatever the molecular entity is. But, in pediatrics in particular, it has to be both developmentally contextual organ system and medically addressable, which need to be present.

Finally, I guess I'm showing my age, but when we talked about you being Oprah, I'm going to bring up Janis Joplin. Freedom is just another word for nothing left to use was what we used to sing in the 60s and 70s. It's nothing left to lose. Not quite right. I think we're a little bit more nuanced there, but if you get the nuance there, what are you going to say to a family or a parent when they get a diagnosis of a rapidly progressive disease? There is no stronger motivation than a family to take care of their child. We recognize that. It's intrinsically coercive.

When you talk about informed consent and someone says, "Well, there may be a trial," the family is coerced into thinking I have to do this for their child. There is really no way around it. Parents usually get it right. I for one would never want to be in a situation where I had to be big brother and substitute for a parents' right to know what was best for their child.

Skip Nelson: Okay, let me broaden the discussion a little bit by throwing risk and uncertainty, which we've alluded to into the equation here. The question is, what's the amount of information? You alluded to animal models and to other information. But I'm going to go back to Phil, and Mark, and to Holly, and to say, as one who's thinking about enrolling a child in a clinical trial, what are you looking at? It not only the hope or the benefit that you hope to achieve, but the information about the possible risk. The child could be worse, or there could be

other things. What kind of information would you want to see? What did you look at in fact as you made the decisions to have your own children participate on that risk side?

Mark Papier: That's a great point. We don't want to make decisions as a family out of desperation or coercion. My wife Tara and I, when we met with Dr. Porter and he discussed some of the risks involved in the trial including the hearing loss, we had to have surgery to insert a reservoir in the brain. Every month he has to go in for a spinal infusion. You don't know how is this going to affect our son, how is this going to affect his quality of life.

The alternative of course is that we don't do anything. We're caught between a rock and a hard place. As a parent, we had to trust our doctors. We're fortunate to have the NIH working on this disease, Dr. Ory and Dr. Porter. That's who we put our faith in. They explained the risks in great detail. Again, we don't want to act out of desperation, but we're going to be willing to do what our doctors tell us to do. I am not a scientist. I'm just going to put my trust and my faith in the doctors.

Skip Nelson: Let me then put Danny on the spot. You are now aware of this faith if you will. The obligation then is on you to decide whether you go forward or not. What are you looking at to decide that's a risk you're willing to take in advising Mark?

Daniel Ory: Yes. I'm going to go back to a little bit of anecdote, to one of the phrases that is in my informed consent and became a topic of discussion at IRB. It's simply under the risk of the drug that we don't know, but could result in death or permanent disability.

I'm not sure. I think I always make a point to mention that it's there. But because of the disease that these families are dealing with, it's never been a discussion. It was an interesting discussion of the IRB because they said, "How can you put this in there? There will be no sign up." It's a very different perspective. I think it was being honest that this is an experiment. It's a very unlikely outcome, but it's there.

How do you weigh the risks? I think we have to come back to it's a concept. I think you establish what risks are likely. With this particular drug, in the animal models it's clear if you go high enough you will cause permanent irreversible deafness. We think that there's a potential of a therapeutic window between the dose we need to use and the dose that would cause deafness.

The approach that I use is I think you have to think about it as, how do I mitigate that risk, how do I minimize it? That's I think done by designing a trial in which you're not only carefully looking for efficacy endpoints or focusing on or the biomarkers doing what you want to do, but also have you built the trial in a manner that you think that you can do it safely where it's if you're starting to get into trouble, you can back out before you have risk?

I guess, I think of it in terms of trying to mitigate the risk as much as possible. I know I need to express those risks to the parents, but it's very hard to ask the parents to weigh that the same way that I need to do as an investigator as a physician, because they're in a situation where the outcome is really clear to them. I guess the answer to your question is to try to understand it as much as you can. Then, mitigate the risks that are there.

Skip Nelson: Alex would like to say something. Then, I'm going to turn to our FDA colleagues after that.

Alex Dorenbaum: When I started in medicine in residency I thought I didn't know anything. I was afraid to make decisions. At one point in my career I was cocky and I thought I knew everything and I should make all the decisions. Now, I know that I have to share those decisions with the patients. There is no … I will not allow in my daily decisions when I see patients for them to say Dr. what would you do? I go back to what … I loved one word you said. You said, "When we were given the diagnosis."

What that means to me that this is not a disease of a child, this is a disease of a family of some sort. In essence, all diseases are diseases of the family, the diseases of children and adults, and all diseases as families. In the same manner, I don't think the decision is my decision as a physician. I think it's the decision we share and the burden we share to make this decision. It's a shared responsibility in my opinion.

In my mind that's the key element. It's really forcing the relationship to be a co-operation. That it's probably not that different from our relationship with the regulators that are making these decisions, and it's not different from the decisions we have with the investigators from a pharmaceutical perspective to engage with investigators that are going to do the research. It's a shared responsibility.

I have to say, in terms of safety, toxicity, and efficacy I mentioned I worked in the HIV programs early on. I actually participated in the first trial in children with AZT, the first drug that was given to children. In those days, the expectation of survival for a patient with HIV were basically zero. In fact, all the children that we treated with AZT didn't make it because AZT alone was not sufficient to control their disease.

But, in those days, when I was working at UCSF I had about maybe 400 children with the infection. We were losing about 40 children a year. UCSF has not lost a child with HIV in the last 5 years. The advance that has happened in treatment and the benefits that children have today in terms of therapy for HIV rests on the work we did with families 20 years ago. For me, I live with the decision that some patients received suboptimal therapy. It's not an easy decision to make. It's not a decision that I feel comfortable with making alone. I share that decision with the patients for that reason.

Skip Nelson: I'd like to frame a question for Andrew, and then see if our other FDA colleagues have something to add. The IND application has now come in. The community has gotten together and they've designed a trial they think is appropriate. The investigators think it's ready to go. The advocacy groups are ready and waiting. In it comes in all its glory with the data and support of it. Animal data. There's no adult data and whatever. I guess I'd be interested to hear how you think about such an application coming in in this space, rare pediatric disease, no adult equivalents. Animal data at best, animal models of variable usefulness in terms of phenotypic variety etc. What are your thoughts on how you would evaluate that?

Andrew Mulberg: First of all good morning to all. I'm Andrew Mulberg, Deputy Director of Gastroenterology and Inborn Errors Products here at the FDA. I've been a partner both in pharmaceuticals and academics, and now government, and I think that one direct answer to your question is that I certainly hope that the partnership before that IND has arrived, had has extended to us as partners. Because the IND process which we're not going to go through has certain regulatory rigmarole attached to it in terms of functional review of various components. But what makes it greatly facilitated and having been part and continuing to be part of the evolution of Dr. Porter and Ory's program with the families has been involved in hopefully helping to craft a program that will be acceptable from the regulatory perspective from the outset.

One of the greatest frank disappointments for me is for us as colleagues, both Dr. Lee and the whole division that's not represented here is not to be involved early enough. I can't stress that enough. The answer to Dr. Nelson's question is that we are going to hopefully approve that IND to go forward, and that's the perfect world.

That's greatly facilitated by having communications with partners from the beginning summarized by all of the previous speakers. That's too general of an answer for you Skip, but I'll leave Dr. Lee to answer it more specifically, but generally that's how I would respond.

Skip Nelson: Lynne or Jessica, anything you'd like to add?

Jessica Lee: Is there anything specific you'd would like me to address?

Skip Nelson: No, no, just your thoughts on that.

Jessica Lee: I think Dr. Mulberg has outlined it very nicely. Just as a brief introduction, my name is Jessica Lee. I'm one of the clinical team leaders in the division of Gastroenterology and Inborn Errors Products. As Dr. Mulberg said, we would like to be involved as early as possible and I cannot emphasize the importance of natural history enough. Because especially in these rare populations if we know what to expect and what patients have and what their functioning is

and how they would decline, it really helps us to really understand better how we can really help develop a drug that would be most beneficial for patients.

Often times we go through this all the time where a lot of drugs for a lot of these diseases, there is no adult. We want to try to minimize the risk to children and we want to try to study adults first. But, they're not really applicable for a lot of our younger population who progress a whole lot quicker and they don't behave anything like the adults. Adult data are less useful.

Then, we get some animal data. If there is a disease model that's great, but sometimes we don't really have that information either. This is why we think that natural history study is important. I understand the drugs are really in development. I'm hoping that going forward for any of the other rare diseases if we can start that early on and we can partner together and try to learn about the disease, learn the mechanism of drug, to be able to help design the study in a collaborative way. If we don't have all of the information, we just have to make some with benefit assessments and make sure that there is a good safe monitoring in place so that we can try really to bring good drugs to patients as quickly as possible without doing undue harm to our patients.

Skip Nelson: Thanks. Lynne. Then I'm going to open it up for the audience. Hopefully you all have been thinking about this subject. We'll go from there.

Lynne Yao: Hi, my name is Lynne Yao. I'm with the Pediatric and Maternal Health Staff here at FDA. Actually I'm impressed with the number of people who are here today, specifically to talk about rare diseases in infants and children. As I was having a conversation with some of the folks in the audience, and I know, yesterday's meeting was rare diseases, which is already a process and a group that is very special. Often, again, there's not enough attention paid. You move that up to rare pediatric diseases, that cone is very, very small. All the problems that folks face, academics, patients, regulators, government, investigators, that whole community of people are trying to figure out how to treat kids with rare diseases, that all of the problems related to drug development get magnified to the population we're talking about today.

I really do appreciate everybody is here. We really do want to hear everybody's feedback, like how we deal with this very, very specific population. As it relates to the conversation at hand, which is how do we assess risk and benefit in this very, very specific population? I think what I've heard clearly is that for every disease it's going to be a little bit different. For every stage of disease it's going to be a little bit different. For every individual patient it's going to a little bit different.

I know that I've heard certainly and accept the responsibility that FDA has 2 speeds. FDA is either too slow or too fast. So, what we're trying to do here and what I hope to get from folks is that how do we make it slower when we need to? And how do we make it faster we need to, recognizing that there is no speed fits all for any program. What we need to do is build a

framework with the information we receive from you about how to adjust that speed when we need to.

For example, in a condition that's rapidly progressive for which we have a lot of natural history, for which we have a candidate product that's been repurposed so that there's all sorts of animal data that may be that speed setting can go a little bit faster in the clinical trials. But for a condition in which we know it's slowly progressive, we know that's going to take maybe much, much time before we have an endpoint that is irreversible, that stabilization is very important. But that we have very little information about a new molecular entity, how fast can we go into that patient, knowing that the risk, if we get it wrong, will ruin it for every patient coming behind them. That if we have an adverse event that is going to kill a program because we went into fast, that all those patients behind that could've benefited won't ever have that benefit because we went too fast.

What I'd love to be able to hear, so I'm not answering anything, I'm asking, is how do we set the speed? What factors do we need to consider as FDA scientists, as clinicians, as parents, how do we set that speed so that what we get the applications in each time we know how to set that dial?

Skip Nelson: Thank you Lynne. I think that's a nice way to frame it. I would like to open it up for the audience and you we're carrying a mike. So I'm going to ask Lynne if she wants to stand up and help. We'll actually come to you. There isn't a television camera there. There's no one that's going to necessarily say so.

Jeff Leider: Hi there.

SkipNelson: Say who you are and where you are from?

Jeff Leider: Hi, I'd like to welcome everybody here today and I'd like to thank the FDA for giving me the opportunity to hear myself. My name is Jeff Leider, I'm from New Jersey, I'm the president and founder of Let Them be Little Times Two. I am also on the board for New Jersey rare, and I'm part of the Hunter Syndrome Research Coalition. My reason here for today is to explain to everybody here that I'm not a scientist, I'm not a doctor, I'm not a powerful person. All I am is a daddy trying to save his little boys.

I sit here in this room yesterday as well as today and I hear about the risk. Well, in my case, my two little boys Jason and Justin who are diagnosed with Hunter syndrome, they don't have time. In Hunter's syndrome the longevity is 10-15 years old. By 15 years old most of our children will pass. I don't have time. When we sit here and we talk about risk, we talk about the things that could happen. I know what's going to happen to my two little boys. Unfortunately my boys are going to die. If there's a situation where somebody would come to me and tell me, that there is a

drug that possibly could help them, but Mr. Leider this drug may actually hurt them, I'm going to take my chances because ultimately I know my children will die in the end any way.

Fortunately there is some things that out there for Hunter syndrome at this point that are actually working for our children with Hunter syndrome. This trial is on clinical hold at this time. If they would've told me that my children could get in it that would be great. Unfortunately they can't at this particular moment because a certain risks that are going on. I just wanted to explain and I wanted to talk about this actually yesterday about the communication between a direct communication between the parents as well as you know … everybody here on our panel as well as everybody here at the FDA.

Now, I may not know all of the terminology of Hunter syndrome or I may not know the big words that were flying around yesterday in this room. I may not know much about the disease, but there's one thing that I do know, that the panel doesn't know as well some of the people here in this audience is I live the disease. I think it's very important that people actually reach out to us and actually ask us, what are your concerns, because we live it 24 hours per day.

Recently our organization published a book that just came out on the market is called, "Walking in our shoes." I will say to everybody when I do a lot of guest speaking, is that don't judge me until you walk in my shoes one day. As we go forward here I think it's more important to understand what we go through each and every single day, 24 hours a day, not just in meetings like this or reading it into some type of a book, and to actually ask us what we need for our trials?

With this risk, this is a very important thing to me, like I said and I'll end here on this point, is that without my children getting this necessary drug that is out there in hold right now, ultimately my children are going to die. If there is a risk to give my children that drug, isn't it better to give them a shot, even though they're going to die anyway. Let's just give them a shot and maybe they have the opportunity that my two little boys Jason and Justin can live and grow up to be normal people, thank you very much, and our journey continues.

Skip Nelson: Thank you for your comments.

Lynne Yao: Skip, I have one over here.

Peter Adamson: I'm Peter Adamson from the Children's Hospital of Philadelphia. I'm a pediatric oncologist and I chair the children's oncology group. My comment in some respect is a natural follow-up to what I think many parents with children with life-threatening diseases feel. I do think we have a culture of risk aversion that is negatively impacting therapeutic development. Let me preface my comment, my question to the panel with the challenge children with cancer face, there are similarities and differences with many of the diseases we face here, and certainly

the timeline of disease progression is a variable, but none the less these are all life threatening diseases, many of these in fact are life-threatening diseases that we talk about.

The very important point that was made is, when we bring something to trial we have to go out of our way to make sure we frame the benefit as a realistic hope for, and not an unrealistic hope. The minute we put cure on the table, the ability of anyone to make an informed decision I think is greatly compromised. I do think we have to be very careful in the terms we use about what realistic benefit is and what can be gained from that. Why do I think there … what is the contributing factor of the risk aversion? Right now, I think risk aversion is at multiple levels. There is risk aversion on the part of investigators, there is risk aversion on the part of the NIH, there's risk aversion on part of IRBs and there's risk aversion on the FDA. This is not just on the FDA. This is I believe in the research community at large.

What I would challenge the people who evaluate these studies, is right now the charges to evaluate the study in the context of the study only, and not in what would happen to children if this study doesn't move forward? Because certainly for life-threatening cancers, and I would assume for many life-threatening diseases, the notion that if we don't have the study, parents will do nothing, is not realistic. Parents will seek treatments.

Some of those treatments are going to be based in science, some of those treatments are going to be in the alternative medicine realm. But, we all know that many, many families will seek treatments, whether those treatments are on a clinical study, or those treatments are something found on the Internet. It will happen. When we look at the research I think we have to look at it in the context of what else will this child experience if this study moves forward? Because certainly the greatest way to avoid risk is not to do research. We would put an end to the discussion of risk related to the research if we didn't do research.

I think the pendulum has to swing and I would ask Skip and others is, when IRBs and others look at the risk, what can we do to try to broaden the discussion of what would happen to potential research subjects, not just when they would participate on research, but if they don't participate in research. Because I think the safety and oversight of children participating in research by definition, I spoke too long, is going to be greater than when they do not participate in research.

Skip Nelson: You must have pressed a button there Peter that you weren't meant to press. Just one quick comment and then we can go on with the discussion. If you look at the ethics framework I'd like to call it, it is a regulation, but in ethics framework it says the risks and benefits, the risk must be justified by the potential for direct benefit. That's one thing. But it also then says that that risk-benefit balance must be comparable to the alternatives. I think in that phrase comparable to the alternative you could begin to introduce a consideration that you have. If there in fact there is no alternative for a life-threatening disease, then that understanding of risk

and benefit should shift that it would from a situation in which is not life-threatening and where there may be other alternatives.

That's where I think there could be some flexibility in framing it. In fact that's part of the motivation behind having this conversation, is to explore that flexibility and to frankly explore the fact that the perspective on this risk ought to be shared among the various stakeholders in this conversation. That's precisely the motivation behind the session. Phil, and then I'll go to this young lady here.

Phil Marella: Yes, Skip. I wanted to address both those points, because Danny reminded me when we sat down with Andrew, you have to realize similarly most kids with Niemann-Pick historically have not made it past their early teens, 13, 14 years of age and we've lost the child. Our daughter Dana as I said was almost 20. Another child we knew who didn't get the benefit of the Zavesca passed away when she was 14. I believe she actually had a more progressive form of the disease that Dana did. That's one of the reasons why we feel she benefited from the Zavesca.

Denny reminded me when he talked about this current clinical trial for Cyclodextrin and he had to bring up the risk of death and all of that, and turn our attention to it for a second. Having been involved with the Cyclodextrin effort from the beginning and when it was first discovered, as a potential therapy for Niemann-Pick C, I almost find that stunning, that IRB would've said, you're not going to be able to get children to enroll in this trial.

This is something that's been used as a solubilizer for a decade or more for different drugs for delivering medicines. No one just realized that it may have its own benefit. That it was a little surprising to me. With the Zavesca it is a different perspective. I think we do have to focus more on the patients and the families. With the Zavesca one of the issues that kept on coming up at the FDA panel review for potential approval was whether or not the drug may be stunting growth. It's a completely different perspective when you're on the outside looking in.

When you're on the inside, if my son Andrew who's 14 right now, he is 5'3", he's only going to make it to 5'5", live to be 40 or 50 years old. I'm okay with that. I was almost stunned that stunting growth came up as an issue. I realize maybe you need to raise it, but I think you raise it, and then you move on. You know? But, I understand, perhaps we need people. It has to work both ways. We have to push, we have to aggravate. We need people keeping us perhaps grounded but from the perspective of a child who maybe isn't going to make it to 10 or 15 or 20.

Melissa Hogan: Hi, my name is Melissa Hogan. I have a son, a six-year-old son case with Hunter's syndrome. Also have a foundation called Saving Case and Friends. My perspective is a little different than my esteemed colleague over here who mentioned that if we say cure it kind of blinds parents a little. But I totally disbelieve that. We're big boys and girls. I just want the FDA to understand that the people who are very cautious about things like that aren't going to

come to try to enter a clinical trial anyway. Parents are reading the research. We know like you said talking about the risk of death. I don't even consider any of the lesser risks. The risk for me is always the risk of death. I say the risk of death is better than the certainty of death that is brought about by the disease.

Our background is my son entered a phase 1 2 critical trial three years ago and had some complications related to device failures. Had to have the device replaced several times. But I've talked with FDA before. I said, I would do it all over again, surgery after surgery after surgery. If he had contracted meningitis and died from that it would've still all been worth it, because it was the risk of death versus the certainty of his death.

Frankly a number of us Hunter parents sat around the other night, and said, you know what, we looked at this risk tolerance issue and we said, what really are the factors that gauge risk tolerance? We came up with a theorem or a scale that we considered that was disease-related as well as particular patient-related based on our communications with our community. We said it was we have the reduction of lifespan created by the disease, the impact on the quality of life created by the disease, and the certainty of the prognosis. If all of those things are worse, that's over the remaining life span. If the remaining lifespan is dwindling that is higher multiplied by the current impact of the disease. If all of those things are there in a disease were a child has gotten older and more impacted by the disease, their willingness to accept risk in a clinical trial is much greater.

I just want the FDA to understand that, that's at least our perspective on how we look at those qualities. I think that may go across the board on a lot of pediatric rare diseases.

Skip Nelson: Holly indicated she may want to respond, and then I'll come back here. Andrew as well. Holly, Andrew, and then …

Holly Peay:I think that's extremely important that parents identify those attributes in patients dependent on the situation identify the attributes that are important and that benefit risk assessment. I think something that we could really use guidance from the FDA, is there are validated measures that can quantify patient preferences. This is a data driven process, this regulatory process, and we can provide data, patients advocacy groups, the CDA is well ahead in this area of looking at how you actually quantify patient preferences.

I think that what we need as patients advocacy groups is guidance from the FDA on what sort of data are you comfortable with? These patients' stories are incredibly strong. They are really I think useful, but they may not represent the feelings of the majority of families. Maybe they do. We do not know.

A data-driven approach would help us to identify where that heterogeneity lies in the population, what's risk tolerance is acceptable in different critical situations. There are very good valid methods to do that, but what we need the FDA to tell us is how to create the model that is reproducible in foundations, in advocacy groups with academic partners to identify those preferences in patients and give you all information that isn't just acceptable to you, but that you will actually use in your process.

That's a model that we do not have. We've got some pilot work there, we've been presenting it to the FDA, but frankly the response we've gotten is very different opinion on who we're speaking to in terms of how useful it will be. That model will allow us as patient communities to rally around a set of attributes that are important to patients and families, and to give you all the kind of data you can use in a regulatory process.

Andrew Mulberg: Thank you. I want to just dovetail to that because it's your organization that has done I think a very leading edge work on benefit risk assessment. If anyone hasn't seen this benefit risk assessment by the Duchennes.org organization, I highly recommend it. Because one of the issues that we have to deal with, that we've been talking about is risk tolerance and understanding the benefit of the risk. Obviously we work very hard, and your document clearly demonstrates how we try to use that algorithm. But it's an evolving issue.

I think what we're hearing from Dr. Adamson and now we're hearing from others, is that understanding risk tolerance has clearly evolved. From the death of Jesse Gelsinger a number of years ago which really to me was a seminal event in the understanding of how ethics can be misconstrued with the issues of coercion were Dr. Caplan made that decision, recommendation that it would be coercive for the infant's parents to make that decision.

Well, as a pediatrician, I've dealt with that issue every day of my practicing life. That is the nature of a parent with a sick child. That is coercion, no matter what you want to do, explain it away or not. I think it's really important that the public appreciates that one of the issues that I feel is very, very strongly about, is that pediatric experts are necessary to be part of any dynamic, they are necessary to be part of the pharmaceutical industry, they're necessary to be part of interaction with patients, and they're clearly necessary in the work that we do as part of understanding pediatric diseases.

That may not go down well, but that is how I think we … that I tried to espouse the work that we do in our division with experts like Dr. Lee and the hoard of individual experts that no one ever sees. The dynamism, the interest, the passion that is completely devoted to all the issues that everyone here is … and that's why I've invited you all, to invite us to be part of your programs as Dr. Lee also stated. Get us involved early in the program development so that we don't spend a lot of time redoing programs that we could've easily done the first time, maybe more easily. not necessarily perfectly, but easily. That's just my only comment about that.

Skip Nelson: Thank you Andrew. Before I go to this young lady here, I just can't resist making this one comment. Coercion really is not the right word to use here. The concern is whether you're under the influence by the fact that your child has a life-threatening disease. If you want to read an argument that I says that that is not a good argument to say the choice is any less voluntary, I recommend you look at the American Journal Bioethics. I think it was 2010. First author is Nelson. Second author Tom Bicham. It's on the concept of voluntary choice. By the way funded by National Science Foundation and NCI just so that in my pre-FDA academic work, but anyway. We developed an instrument to measure which parental choice is voluntary, which I would love for people to include. It doesn't cost anything so I get nothing from this. There's no conflict of interest.

Amy Miller: My name is Amy Miller. I'm here with my husband Gray and my son Danny. Danny is 17 and he is severely affected with Hunter syndrome. I know it's a lot of us speaking with Hunter syndrome. What I wanted to say as some of the other dads on the panel said, it is progressive. It is fatal. At this stage of Dan's life we are probably in the latter stages of the disease. I think what's unfortunate is that we all do want a cure. But our biggest goal for him when treatment did become available with enzyme replacement therapy was quality of life. There is not a way to measurably measure that for your standards.

We accepted quite a while ago that quality over quanity for Dan, that's what wanted. We know someday there will hopefully be a cure. What I think other people here also need to understand is some of the diseases and how they are carried like Hunter syndrome are excellent. The natural history study we participated in while ill appraised, was being clinical trial many years ago could potentially help a grandson of mine because we have a daughter and we don't know if she is a carrier.

Even though these things may not help our child, it will help in the future for everyone. As you can see, what Jeff said, it is a devastating disease to watch. We went from seeing a little boy who could run, play, eat, laugh, to a child who's completely 100% dependent for everything, tube feed, and can't even pull his covers up at night if he's cold. I would commend you for all the work that you're all doing. I appreciate it. Thank you for helping to give quality to our kids.

Skip Nelson: Thank you.

Speaker from Audience 1: My name is [inaudible]. I'm the head founder for a small biotech company. We do research in many things, including rare disorders with the stem cells. I think that the underlying question in this conference is, can we do something more for rare disorders? I have a couple of suggestions that apply to FDA.

In my humble opinion FDA has been doing something in the sense of clearly and in defying that rare disorders cannot be treated like common disorders. This is evident in the way the FDA is

dealing with the surrogate markers, were the likelihood of a clinical benefit is certainly a lower standard that you would expect from a common disorder. But I think the agency could do a bit more. My general recommendation will be to continue under that and trying to do more.

For example, entering rare disorders, when you start not only you have a very small number but also you have no natural history, you don't know exactly what happened, and you don't have clinically validated instruments to measure the pro-risk or the duration.

Small sponsors, parents, and society cannot wait 3, 4, 5 years until we do the good, solid natural history study and then try to start a people profile. I've seen the agency trying to go along with that and doing things in parallel. But the validated scales are the same. There is a process for patient reported outcomes that applies very well for common disorders. We cannot request that for rare disorders. It would take forever to do what needs to be done for a common disorder.

Finally, another general suggestion is that one of the challenges the sponsors face in the agency is the dispersion of knowledge. If you have a small molecule for a serious disorder you will go to CDER, the early division. If it's a biologic, a little bit different. If it's a stem cell gene therapy, its different. There might be a way to harmonize a little bit more the knowledge that the agency has around divisions with respect to rare disorders.

Lawrence Charnas: I'd like to go back to the previous session when we were talking about what does a network look like. This may sound advice of Dr. Mulberg, I asked if it was okay for me to say this. Any essential network has to include all the partners in the matrix. That means has to be the patients, has to be industry, it has to be the researchers and it has to be FDA, and they work together in a matrix organization and they each bring together very specific knowledge sets and processes that are critically important.

I work for a rare disease company and I have to say that the FDA has demonstrated extraordinary flexibility. They're not always knowledgeable in the beginning, but they get up to speed pretty quickly. That's the role of the interactions. They really have the patient's best interest at heart. Before they came to FDA, their physicians and healthcare providers and they really have the best interest of everyone involved. They sometimes have to make difficult choices. Do you take a promising drug and administer in such a way that you can't go forward so that a risk ruined a potential benefit for lots of people? Nobody wants to see that selfish choice. These are extraordinarily difficult decisions. I really do want to commend them for the work that they do. This is a thankless job. At least someone publicly should say thank you.

Ciara Kennedy: Ciara Kennedy from Lumena Pharmaceuticals. I wanted to build on the point that you just mentioned about patient reported outcome measures in rare disease and to bridge on the point that was just made. By getting the FDA involved early in our programs and working very proactively with the Seal division, which has been a wonderful resource for us, we now

have an instrument that we take forward into clinical trials. It feels slow at the time. You feel like you're being slowed down, but it's a really worthwhile investment to have that dialogue and put in that ground work.

You can go faster at the end. We talked about when to go slow and when to go fast. It takes a lot of effort to come up with an endpoint, an instrument that measures something that patients' care about, the parents care about, the physicians care about. But we're now at the point thankfully because we've done that work that we hopefully can go fast and we'll know if we're impacting something that's really clinically meaningful for patients.

I just wanted to bridge on the FDA and the seal division in terms of a common disease, yes, the hurdles and the size of a dossier that you have to produce is enormous. But they are very accommodating for rare diseases and will work with you knowing the size of your patient population, and come up with what's sufficient to know that what you're presenting is real. But not put so many high standards above you that you can't move forward.

Skip Nelson: Thank you. Just to say one thing so I don't lose the thought. It occurred to me given the comment about quality of life and the emphasis on quality of life. That's one of the more difficult things to measure in a parent reported outcome, even worse in a physician reported outcome I'll say, but certainly in the parent reported. It occurs to me there may be some phenotypic similarities across roots, even if path physiology or genotype is different, that maybe there are some parent reported outcome measures of quality of life that could go across what's Seal I think would call context of use.

If there's phenotypic similarity among groups that a tool could be potentially used across programs. There's a question mark at the end of that. I do not develop this so I don't know if the answer to that is yes or no. Andrew, you may want to comment?

Andrew Mulberg: I do want to comment because this is an area that I think really does require a little bit more discussion. Unfortunately none of our Seal colleagues are here currently. But I just recently sent an e-mail exchange with one of the senior members of that specifically on the topic on a nearly developed PCOR instrument, looking at pediatric quality of life as well as a subscale of a promise instrument looking at fatigue.

Fatigue for instance is an interesting concept because it does come across, intersect across many diseases. I guess I would say Skip that, one of the issues that is evolving that is important for us to further discussion on is the one you just raised and to the credit of a parent who raised it as well, which is how can we use quality of life in some proactive way? I don't truly have the answer, but I know that I've heard this before and I think we are trying to evolve that at least in some of the diseases we're dealing with. Again, I would invite another public discussion of this, and I will bring it back to our Seal colleagues.

Skip Nelson: So let me … Alex has a comment to that. But let me then, I'm going to spend about five more minutes and I just want to measure if there's someone who feels they want to say something, that they've had a chance to say it before the end of the session. So one hand, but I just want to make sure. I see three hands. All right. I see four hands. No more hands. Alex keep it short.

Alex Dorembaum: Very short. We're incorporating in our clinical trial a very interesting question. We're incorporating the question of given all of the mishaps and the problems and the discomforts and issues that came into participating in this study, and the benefits that you feel you may have achieved from the study, would you do this again? We're trying to get to that core element of understanding that as the great coach said, "No pain, no gain." But the gain should be superior to the pain. We're trying to distill that question and understand it in our clinical trials. I don't know if we'll do it well or not, but we're trying.

Anil: My name is Anil. I'm with the US in Life and we develop small prototype devices. My real question is, we're hearing a lot about progression of disease and quality of life. How do you measure progression? Obviously we need more biomarkers, we need probably more instrumentation. But just an open ended question, what do you call progression of disease and how do you measure it? Or do you just leave it to the parents and say scale it on from 1-10, with the disease progressing quickly?

Skip Nelson: I regret this. I don't know if we're going to be able to answer that in the time. Let me get the other questions so we have a moment for comments after that. Go ahead sir if you want to ...

Charlie Richard: This is Charlie Richard again. I was just going to tie together some things here people were talking about natural history and also risk benefit. I just wanted to point out it's extraordinary to me that the natural history study that I did over three years the dedication, effort of the parents in the study where there was actually no benefit of a drug, but they were willing to participate, coming to a central place twice a year, and participating at in the hopes of a drug being available later.

At the end of the first year, and that was just a one-year study, I thought we were going to wrap it up, and the parents actually came back and said, "We need to keep on going on this. We need to keep doing the natural history study." They were absolutely right, and we were delighted to do that.

I think the other comment about what was difficult for me and it speaks to the dedication of the parents I think, as you move in to maybe the third year of a rapidly progressive disorder, some of the parents have come and said, "I realize that my child's progressing too fast to actually be in a

study." It's parents that are willing to be in a natural history study for several years, who then understand that the benefits are much less.

The last quick comment I wanted to make is just to re-echo what other people said about patient reported outcomes in natural history studies. You have to start really early to do that. I just wanted to make a comment about some indulgence for pharmaceutical companies about, why don't you do this early? I remember the first time in 2006 I approached my boss about this. He said, "Well, this is a project buried in the pipeline. We're going to develop a new enzyme replacement therapy for this disorder."

I said, "Okay, the first thing I need is $3 million to be able to do a natural history study." Going forward he said, "Wait a minute, we don't even know if we can make this drug. We don't have anything else about this. You are wanting this money early in the study." And I said, "If you don't do the natural history study now, it will never get done, because once the drugs are available, then it's impossible to do that." Of course we realized that's true even for some of the marketed drugs now where people in registries are searching for comparative groups, but you're never going to find those patients, unless you get started early in natural history study. Thank you.

Stephanie Bozarth: Hi, my name is Stephanie Bozarth. I'm with the National MPS Society. I'm a board director. I also more importantly have a daughter with MPS4, which is also in the same family. We're obviously a very passionate group. I actually wanted to bring up the question to you about with the MPS diseases, we've had enzyme replacement therapies for 3 of our 11 MPSs and all 3 of those trials and there is a fourth one that is currently in FDA approval, which my daughter is in, they all started over in Europe and UK. Those were the phase 1 and phase 2 trials. My understanding is it's more than just globalization of clinical trials.

There's so much animal study toxicity studies done, prior to these getting these trials started, that it's costing more and more. This is just one more obstacle that's preventing more enzyme replacement therapies getting to these kids quicker because it is progressive, and it is important. And when it goes over to Europe and the UK, 2 years for an MPS patient and many lysosomal disease patients is 2 years too long. They might not be alive in 2 years and the disease progression might be gone too far.

It's really just something that I hope that the FDA will take seriously. And look at how we adapt the guidelines on harmonization. And how Europe and UK and maybe take some notes from how they are able to start these trials so early and they're having success there and then they're able to pull them the Phase 3 over here. How can we move those trials into the US? It's US companies, it's workers, it's US families that are funding a lot of this research. We want our US kids to have some first access too.

Skip Nelson: Great, thanks. Last comment. Let me do say, the FDA is taking that seriously. A follow up comment and then …

Lori Sames: I'm Lori Sames, with Hanah's Hope Fund. I actually stood up to speak before the oncologist spoke. After he spoke I decided to sit back down until I heard the word coercion again. When is death imminent for a cancer patient? When is death imminent for a child with a neuromuscular disorder? In the case of my daughter's disease, Giant Axonal Neuropathy is the next bout of pneumonia. We weigh in quality of life, we weigh risk benefit. Chemotherapy drugs are very toxic. We have a teenager in our home town who had lymphoma. They chose to do another round of chemotherapy. One of the side effects was a possible brain bleed, he died of a brain bleed. Death for him was eminent, was it 18 months? Was it 4 years?

Under muscular disorder we have 11 year old that spent 2 and a half weeks in ICU, part of the time in a drug induced coma, nearly died of pneumonia. If he doesn't have another bat of pneumonia, he could live to be 18, and die then of pneumonia as a quadriplegic, then dependent, feeding tube, lose the ability to speak and swallow.

I was going to save this for later on, but I think I'll do it now very quickly. I hate reference to the Jesse Gelsinger case. It was brought up yesterday, it was brought up today. I read about it a little bit more last night. They're still not sure why he died. Yesterday some misinterpreted, monkey data was mentioned. I read last night, it was actually a different factor in a different dose for the two monkeys that got sick. In my mind, in my opinion, it started with the bioethicist who decided that going in a child would be dead by the age of 5 would be coercive to the parents? Wrong. The child was going to die anyway. Jesse was the 18th patient treated. Patient 17 got the same dose. Would've, could've, should've. We always remember history so we don't repeat it.

But there's 2 last points I want to make. Had they gone into a 5 year-old which probably would've been fine, maybe the 18th 5 year-old would have died, would it had made world news? Would it have stopped the field of gene therapy for 5 years? No, it was a child that was going to die anyway, and it was parents' choice, not coercion, choice for an option versus definite death.

Lastly, I think we need to be very careful when we reference the Jesse Gelsinger case, because there were so many things wrong with that. We've learned from it. The Recombinant DNA Advisory Committee is in place, they review all assent and consent forms. We've learned, we have moved on. But when we reference it and throw it out there for uninformed parents, it scares them.

Sharon King who runs Taylor's Tail for Baton disease she wants to get behind a collaborative coordinator gene therapy project and she's had Baton parents tell her, "Oh no, we're not going to fundraise for that. There was that kid Jesse that died." The field of gene delivery has come of age. There's amazing things happening all over the world. But it's scaring communities from

pursuing it as a potential option. It's an option for many of these horrific diseases. 85% of the 7000 are ultra rare, I mean 600 patients or less. The vast majority of those are horrific disorders killing children. I just wanted to make those comments.

Skip Nelson: Thank you, and thank you for your passion. I will point out that the fourth session today is on gene transfer. I personally do not use the word therapy in talking about that. Gene delivery will be fine too. When I planned this session just in closing, I characterize this as an appetizer, in the sense that this is a conversation that we've just have begun. It's been ongoing in different ways, but there's a lot more that can be said, and a lot more to be done.

I thank the panel for their participation. I thank the audience for your participation, and I think, lunch, we should have, we want you to come back a few minutes …

Dianne Murphy: 12:40.

Skip: 12:40.

Dianne Murphy: 12:40.

Skip Nelson: I'm hoping they're out there selling some lunch, but I don't know. Are they? I hope that they're there today. But we'll find out.

Skip Nelson: Thanks and we'll be back at 12:40 to work with this case.

Session Eight
Pediatric Oncology

Dianne Murphy: At the end of the day, I wanted to let you know that you will not have to listen to me for an hour. I've asked each one of the session chairs to provide a 5-minute summary and then I will summarize the summary. Mostly we wanted to provide you with some takeaways or what we think we heard today and where we think we hope to go and what some future activities may be. We will try to get that done at the last session. Okay, where is Greg? Okay. Master of ceremonies, it's all yours.

Greg Reaman: Well, thank you. The panelist can probably find their names on the chair. As Dianne mentioned, we'll continue this format to increase, facilitate audience participation as much of participation as much as possible. I am Greg Reaman. I'm the Associate Director for Oncology Sciences in the Office of Hematology Oncology Products at CDER here at the FDA. I am a pediatric oncologist and prior to my coming here a couple of years ago, I was a chair of the Children's Oncology Group for 10 years. I come with a bit of a background in understanding challenges and what we're hopefully not going to do is actually recount challenges but actually try and come up with some opportunities to effectively address them. I think cancer is unique, is a rare pediatric disease because it's not a rare pediatric disease, it's actually a complex of rare diseases and I think despite its rarity, the fact that it is the most common cause of pediatric mortality from the stand point of disease. I think it's without question that warrants our attention.

I think there are some definite unique opportunities that we have in pediatric oncology and that we have a clinical practice model that really has integrated care with a clinical research for now many decades. So, in listening to much of the discussion yesterday and even some of the comments earlier about natural history, I think we have an incredible resource of natural history data on a variety of pediatric cancers. We have also been able to and maybe not as well as we would like to really leverage adult cancer drug discovery and development. Unfortunately, development of pediatric specific products is something that we would clearly like to see more of, there is certainly elements that are beginning but I think most of our history is really in evaluating products that were originally developed, marketed and used for adults with cancer.

Into some extent, we've used legislative initiatives and they've been helpful. Not quite as helpful for a number of reasons. Primarily because the cancers that children get are distinctly different from the cancers in adult so the pediatric research equity act of pre-mandate for evaluating agents is really not relevant for children with cancer. I think in the treatment of children with cancer in the clinical investigation of children with cancer, there has been a long-standing involvement, if you will of patient advocates, parents, families in much of the decision making certainly as far as clinical trial design for large cooperative group of phase three studies, there's abundant stakeholder input and for the purposes of this workshop, I extended that and sought the

input of a number of advocacy groups to try and come up with a list of specific points that we would really like to address during this time that's allotted to us.

Hopefully there will be some additional points that will come up and I would certainly welcome additional comments from you as participants. But they really relate to a number of issues, some of which have already been mentioned and that's defining clinical benefit and what is defining clinical benefit for children with cancer. The definition of risk in life threatening diseases, I think there was abundant discussion about that in the session earlier but I think the problem that I have perceived personally in pediatric oncology is not so much of the definition of risk but its variability and perspectives of risk and the confusion that surrounds the concept of risk. Patient risk, patient population risk, individual patient risk, investigator risk, institutional risk. Is it toxicity and is it risk from the stand point of a drug development program?

I think addressing each of those perspectives is important. Looking at endpoints and again the gold standard at the FDA is in defining clinical benefit and specifically in drugs that are directed towards cancer is prolongation of survival. Looking at overall survival which is the gold stand point or surrogates that are likely to predict overall survival like progression of free survival and I think there are issues that could be addressed in pediatric cancer that might be appropriate as either intermediate or surrogate endpoints. Lastly, given the rarity of cancer globally, I mean broadly and the specific diseases that constitute cancer in the pediatric age group, the necessity for international collaboration and the fact that the drug development is certainly a global enterprise harmonizing as best as we can and I apologize for the use of the word harmonizing, but navigating the differences in regulatory processes and procedures between the FDA and the EMA to make sure that there are not unnecessary delays or clearly something that need addressing.

I thank the panel for their willingness to participate in today's discussions and I think maybe we can start by allowing them to introduce themselves and then we'll move on. Maryam, maybe we can start with you if you don't mind?

Maryam Fouladi: I'm Maryam Fouladi from Cincinnati Children's and I'm the chair of the Pediatric Brain Tumor Consortium.

Nancy Goodman: I'm Nancy Goodman. I run Kids versus Cancer. We drafted and advocated for a creating hope act.

Lee Helman: I'm Lee Helman. I'm a pediatric oncologist. I was actually trained in internal medicine but I've been doing pediatric oncology for 30 years. I'm also now the scientific director for clinical research at the National Cancer Institute.

Brenda Weigal: I'm Brenda Weigel, also a pediatric oncologist at the University of Minnesota and chair of developmental therapeutics for the children's oncology group.

Susan Weiner: I'm Susan Weiner. I'm the president and founder of the Children's Cause for Cancer Advocacy and also a vice chair of the Children's Brain Tumor Foundation in New York City. Our Washington based advocacy group does education and policy analysis on drug development and issues for survivors.

Holcombe Grier: I'm Holcombe Grier. I'm a pediatric oncologist at the Dana-Farber Cancer Institute and Children's Hospital. Former president of American Society for Pediatric Hematology Oncology and I'm here at least in part representing that group.

Malcolm Smith: I'm Malcolm Smith. I'm a pediatric oncologist at the Cancer Therapy Evaluation Program at the NCI and our program is one that supports the children's oncology group and Pediatric Brain Tumor Foundation, another childhood cancer related research.

David Arons: I'm David Arons with National Brain Tumor Society where our national non-profit organization working to find new therapies and a cure to brain tumors for adults as well as pediatrics.

Dianne Murphy: Dianne Murphy, pediatric infectious disease physician who spent too many hours with children with cancer. Came to the FDA to help find some therapies for kids with HIV and have been here ever since and now, Director of the Office of Pediatric Therapeutics.

Peter Adamson: Peter Adamson, a pediatric oncologist for Children's Hospital Philadelphia and chair of the Children's Oncology Group.

Anne Willis: Hi. Anne Willis, long-term Ewing's Sarcoma survivor and I'm director of the Division of Cancer Survivorship at the George Washington University Cancer Institute.

Robert Iannone: Robert Iannone. I'm a pediatric oncologist and I worked at Merck in Oncology Drug Development.

Howard Fingert: Howard Fingert. I'm a medical oncologist hematologist. I'm a senior medical director at Takeda, the millennium side of it, the oncology company and I've had the privilege of working with some of the people here on development of pediatric oncology drugs, both approved and experimental. I am currently the industry representative of the ODAC, Oncology Drugs Advisory Committee.

Greg Reaman: I want to talk in both of these but probably because I'm going to feedback this way anyhow. One of the issues that I think is a little bit confusing in pediatric oncology and as far as new drug development is that we are sort of caught in a paradigm that has been, I think

very successful over a number of years in improving upon outcomes for children with cancer. For many, for most, cure actually is a very reasonable expectation. Having said that, now that we've been able to do that for several decades, we recognized that that cure for those patients comes with considerable cost in a large number of cases and two thirds of patients with significant disabilities and long-term side effects and then half of those situations, life altering and potentially life threatening.

Finding new treatments even in those diseases where there is an excellent likelihood for cure with current therapies is a problem or a requirement for us. At the same time, there are a number of diseases or at least stages of diseases, clinical conditions of a specific diseases for which we don't have effective therapy and looking for effective therapies in the second line and third line setting that demonstrate activity and then eventually moving them into front line treatment trials is something that we have done historically. But I think when it comes to the agency and to our office that reviews or ultimately approves new drug applications. We're sort of caught in the adult model if you will from the perspective of looking at end points and looking at clinical benefit and that clinical benefit for the most part is prolonging survival in patients for whom there is no real likelihood of cure.

We start the same way in pediatrics with the expectation that we will move those drugs forward but I guess, I would ask, are there opportunities that you see for looking at developing drugs that may be for not necessarily resulting in cure but for improving progression of free survival. Improving quality of life prior to progression and how would we actually exploit those opportunities? From a parent-patient perspective, I would actually, Nancy if you wouldn't mind just commenting on looking at clinical benefit other than how we would define it as prolonging overall survival or achieving curative steps?

Nancy Goodman: Sure, thank you. I think patient reported outcomes can be valuable as a set of endpoints for pediatric cancer trials, a child who is 3 or 5, an extrovert day really matters, being able to run or go to school is important for kid as opposed to staying at home. This kind of qualitative measures I think should be seriously considered for pediatric cancer drug development.

Greg Reaman: Thanks. From an investigator perspective, Malcolm, can you just maybe or Maryam actually since ... Oh, thanks. This line is a little bit longer on me.

Malcolm Smith: Yeah, Nancy has just said points about it would be wonderful to have another year to have improve quality of life, count the balances in terms of pediatric drug development and the ultimate kind of eyes on the price goal of more cures for children with cancer is do those come into conflict and the cautionary note that I would raise would be the relapsed refractory setting or cure isn't an option, has been where we've developed the treatments that we can then move up front and try to affect cure and children and if we are doing larger trials that are focused

on different outcomes, perhaps different drugs and relapse refractory setting. Is that going to conflict with our ability to do the pilot space, to do the studies pursuing a new treatment options for cure that historically those clinical trials have been done and the relapsed refractory setting.

I would be just cautious about following the adult paradigm of doing relatively large clinical trials looking for a few months PFS difference or a few months overall survival difference when in pediatric cancer, we really are. Our primary goal is going to be to try to achieve cure and we don't want to start processes in motion that would inhibit or limit our ability to meet that goal.

Greg Reaman: I guess I'm not suggesting that we change the paradigm but I think there's some potential issues or not potential, real issues with the current paradigm given the timelines that are required to do what we would currently do. My question is really not necessarily replacement but are there opportunities to add exploit, because the common refrain is that there are very few new drugs approved for pediatric cancer. There really are very few drugs have approved for the treatment of pediatric cancer when there's a curative intent, but are there some drugs that we might want to consider looking in a setting other than when we are looking at cures, the ultimate endpoint.

Malcolm Smith: I guess like others talk as well, it would be wonderful to do that. The caveat would be, if those are going to be larger clinical trials that are going to spend five or six years in a population that's been preventing something us going two or three trials in that population, smaller trials, then that would be the invested tradeoff that we have to at least be cognizant of before embarking on that but if we can work in different endpoints within the current system and identify something that was effective, that would be wonderful to be able to do that.

Greg Reaman: Brenda, did you have a comment?

Brenda Weigel: I was just going to say, I think Malcolm just touched on this and I think it's been raised on the other sessions that I think we need to have validated tools to measure what we want to measure and if that's quality of life that fits pain if it's a biomarker, if it's an imaging endpoint. I just don't know that we have all those tools at hand in a validated way to make some of those predictive decisions at this point in time but that maybe a goal and that maybe something we really need to strive for is to implement some of those more novel tools in some of the earlier phase, trials because we've frankly never in a systematic way even asked those questions. To get to what Malcolm's saying is I'm not even sure we have the tools right now to actually answer some of those questions and that maybe something we have to really think about exploring and adding to our trials because we may be making a significant impact on quality of life, on pain, on daily functioning, in many ways.

Also looking at progression free survival in different diseases is going to be very different and the challenges and some of those different diseases, particularly diseases like neuroblastoma that

can have very long periods of stabilization are very different than looking at some other diseases that have very rapid decline, particularly some of the brain tumors and so understanding some of those nuances is going to be very important. I'm not sure there's going to be a blanket approach for all diseases and all types of therapy but we need the tools.

Lee Helman: Greg, maybe I can ask you because from an FDA perspective. I think one of the things clearly in oncology more were watching a revolution occur. Our understanding at the molecular level of what drives certain cancers now, unfortunately in pediatric cancers, we're all too well aware. There aren't a lot of smoking guns here. However, one of the issues has become commonly talked about and I thought a lot about it in this morning's session where the discussion about the unusual responders and probably most of us have run small studies, phase two studies where maybe the response rate is 10% but two patients maybe prolonged their life two or three years. I think what our model is not prepared to do is study those patients and try to figure out, why did those two outliers, why did they response? Can we figure that out? Can we take a drug that may prolong the life in a small percentage of patients but definitely did, how do we move forward or should we move forward or continue to study that drug? I think it's a big question mark that the field has to address. I don't know if the FDA has had discussions about this and if you all have any recommendation.

Greg Reaman: I think clearly we look to you for that kind of advice in it but I don't think there's anything from an FDA perspective that would limit that kind of approach. Obviously, resources, patient resources, financial resources are somewhat limited so where do investigator and investigator network priorities lie? I think you make a very good point of evaluating outliers and understanding from a genotypic perspective, what might make them an outlier could facilitate the development in a larger population of outliers and not necessarily outliers. It's possible and it maybe that early phase studies would have that sort of investigation or that sort of analysis become the part of those studies. All right.

Howard Fingert: With discussing tools and resources, I think some companies, industry really appreciate that they have resources in terms of the explosion of knowledge of chemistry, understanding new targeted agents and new biomarkers. I think one of the challenges with pediatric malignancies is how to rationally approach and apply these in the right way with the right trials with the best outcomes? I'm impressed that we talked about moving forward into clinical trials all the time but I'm also impressed with the appreciation that some members here have had for non-intervention research that might really be better enabling to help us to pick the right tools. I know for instance, Kids versus Cancer Organization has been advocating autopsy.

It doesn't sound like it's something very favorable to many of us to hear about but the unfortunate reality is that the major problem often with pediatric malignancies is not what happens with the initial diagnosis but what happens with resistance as years go on, understanding drug resistance, understanding them with the molecular changes, the mutations, the drivers that happen with later

disease can be very important for us to really appreciate how we can best develop combination regimens or regimens that have a crossover design, rational application of the tools. I think that program which I think is just brain tumors deserves a lot of support and I think the Children's Cause for Cancer Organization has been advocating the Carolyne Pryce reauthorization act and that is going to hopefully support biorepositories that will apply also for children's pediatric malignancies.

Again, I think that kind of thinking is also important but I would welcome the thoughts of others here in this podium.

Greg Reaman: Peter, any comment from a cooperative group perspective?

Peter Adamson: Susan, you start while I formulate something.

Susan Weiner: I was going to follow up on the question of endpoints and of really from a parent's perspective, the need for the most current science to inform the design of trials so that I think families would be willing to take greater risks. Greater risks meaning death or permanent disability under two conditions. One is that the design of the trial is enriched with respect of the nature of what the drug was supposed to hit or address. Second, there was deliberate explanation in reassurance about this specific steps and the evidence that was available to mitigate the risk of permanent death and disability that is those specific steps that were taken within the trial design.

This lengthen off the path that you were talking about, it's just that from our perspective, the urge is always to get most finely tuned drugs to the most well-defined population if you can find it out from two outliers, then those kids were worth examining and the drug is worth holding on to.

Peter Adamson: I'll take a minute because I've ... Although most of my work is in pediatric cancer, I've also had experience in the broader rare disease community. Pediatric cancer in many respects is a beast unto itself but I do think there are a lot of similarities with other rare diseases and as Greg pointed out, we always talk about pediatric cancer as if it were one disease but it's actually well over a hundred different rare and alter rare diseases. From the cooperative group standpoint with our infrastructure, we have been able to study childhood cancers with incidents of less than 100 cases a year in the US, so it is feasible. It's not easy. One of the challenges about other end points is that almost all our cancers without treatment are rapidly fatal. Prolonging survival really for the foreseeable future will always be a primary objective because without prolonging survival, you can't begin to get to the important other questions. The children pay far to a higher price for current survival, both short term and long term but if we can't prolong survival, then we won't have the opportunity to ask these other important questions.

Lastly, I want to talk about a little bit about unintended consequences of some of the initiatives, not so much on the US side with BPCA and PREA but in part with our European colleagues. It

really follows this morning's discussion I think in the discussion about Niemann-Pick with so few patients, how do you prioritize amongst ... What study should we move forward? In childhood cancer, we are actually ... We see it's a very similar challenge and the concern about this important initiative which we've had, globally in pediatrics have very positive impact is historically in childhood cancer, we have taken a very disease-centric approach to what state it should be done. We haven't had the opportunity necessarily to partner with a lot of industry partners and we've always prioritized what the leading experts in the disease and patient advocates and so forth would say, "This is the most important question at this moment in time."

As we shift to a very drug-centric view of the world, regulations, it's say, "You have to do studies X, Y and Z with your drug." It's not looking at how we should prioritize that drug amongst all the available drugs or in fact amongst all the available questions that might be important. We're on the risk of moving away from a disease-centric approached prioritization to a drug-centric approach. I do think we have to find a better balance as we work with our industry colleagues and the regulatory colleagues in striking that balance.

Dianne Murphy: I think this is a really important point, particularly for oncology, but for all pediatric product development. For those who aren't that familiar with it, Europe passed legislation in 2007 that is very powerful. Not that ours isn't also, but that you can't submit your adult application until you have a pediatric investigation plan.. The area of most interest toindustry is the adult product development, In Europe you can't submit an application until you have an approved pediatric plan. They will make a decision or decisions will be made, if that product is potentially going to be used in children. So, they are making decisions about products and rather they're going to be used in children and then not letting them submit until they have the pediatric plan approved. Now, we have a monthly meeting with them. Our office coordinates an international monthly meeting where we try to talk about differences and we try to resolve those differences. It's only two hours and we include Japan, Australia, and Canada. We're vicious about time limits but we get a lot done. There is no way we can do all kinds of product development in those two hours.

I think we've gotten closer. Tthe US legislation now is earlier and Europe realizes that they are willing to do a lot of revisions, because their decision about the need for pediatric studies is occurring after phase one in adults, that you have to make these decisions. It is having an enormous, I think, impact and I think it's something that we all recognize because a pediatric world has to work together. There are too many people out there who think they can do pediatrics even if they have no pediatric expertise and then we have to be unified in saying, "Let us solve these problems and let us figure out how do we do this." I think it gets to the issue of how these networks are going to work together globally and work together within the different frameworks because those kind of decisions are going to be made early on. They're going to be made from perspectivesthat may not be a pediatric perspective.

Sponsors are coming in because they want the adult data to be submitted. Now, , that's not always true because some cancers are pediatric only but that's some of the push that's happening here. I think we need to be thinking about that as we develop networks and we need to develop them internationally knowing we have to resolve the trial design issues very early.

Greg Reaman: Okay. I think even though we have time constraints, I think we use the time during those monthly cluster calls to discuss those products in development where there are differences of opinion, if you will or some potential challenges because the European's like in this country, there are waiver request. It's not like pediatric investigation plans are being required for every single product in development for adult cancers, but the whole issue of prioritization particularly when there are more multiple agents in class and multiple inhibitors of the same molecular target is another issue that's going to need to be address at some point by someone or by all of us so we're getting that together. I think we do really focus on those areas because we, has investigators. I say, we, because that was my former life, are very conscious of the fact that we have to work together.

We've worked together on that side of the fence and I think we are actually starting to work together a little bit and now also. Our time lines aren't quite as desperate as they used to be with the FDASIA mandated changes and PREA that now requires pediatric study plans at the end of phase two rather than us asking for pediatric study plans long after an agent has been developed, approved and marketed. Rob, first.

Robert Iannone: The synopsis and the discussion from Peter and Nancy are highlighting the need to think about new drugs, new targets as what potential they might have in pediatric cancer rather than to translate from an adult indication to a pediatric indication or to that same indication in younger kids. I think that's perfectly logical to everyone who's working in the field. For example, melanoma, it's not a big leap to think that if you have a substantial evidence and adults with melanoma or advocacy on a new mechanism, but when you evaluate young adults with 12, 18 in melanoma where the biology is very similar that you wouldn't also have efficacy here and clearly we need to understand how to give that drug safely, dose, etc.

That's not really beyond that need, beyond that need is if that really represents true novel target. Is it relevant in other pediatric cancer where there's a significant aid. With that context, what I would highlight is that the cross cancer development, even though there has been some outstanding successes that we need to celebrate, really the biggest problem remains back at efficacy and failures. To go from Target or a new drug and adults where there's been extensive pre-clinical and clinical research with adult-type cancers, we really need to fill that gap and building a rationale pediatric cancer so we don't spend a lot of time, effort and patients and effort and time in finding failures but rather finding where they would work. I think that really requires collaboration between industry academics and regulatory agencies.

Greg Reaman: Let's just go to the other situation where the failure may not necessarily be in the pediatric disease setting, but there is strong rationale for evaluating a new product in a particular pediatric disease or several pediatric diseases possible but a new agent that is really being developed for an adult cancer doesn't meet its specific endpoints for approval and disappears. How do we approach? How do you suggest we approach as industry investigators, clearly from an agency perspective, we welcome to see these things continued both the active evaluation and development in an application command. How short of the NCI coming in and taking over an agent that's being abandoned, what can be done to actually make it feasible for these drugs which may not approve to be as relevant for adults to evaluate them in children? Can I ask Howard to discuss this?

Howard Fingert: Well, you have to some extent think about this in terms of whether it's a large company that does have other options of other agents marketing or developing or a very small company where those might be their only product. In either case, I think where the agency can help us is to try and understand the opportunity for things like the BPCA incentive or even the approval pathways using the most efficient kinds of trial designs. Now, this is a question at you, Greg, about master trials. Some of you don't know, there's a trend in the larger oncology community towards belief and success of what we call master trials and that's things like, you may have heard of what's called i-SPY Breast Cancer for breast cancer or NCI match study. It's where there is efficiency especially with small populations like in pediatric malignancies because you can bring in multiple drugs either from the same sponsor or multiple sponsors and do a single trial.

The cost, monitoring and startup and all of that is reduced and the patient numbers can be reduced because you can use the same control group if control group is needed at all and you can also then use the results to prioritize one drug over another. There's a lot of efficiencies. Also, in terms of the biomarker there's often times a reality as the new drugs were developing, our match with the companion diagnostic and that also has to go through the regulatory approach to get it approved, to be approved, FDA approved biomarker. The master trials offer a lot of hope to make trials more efficient in oncology but there's a question about how participation in the setting you're talking about, in a master trial would qualify, would satisfy the BPCA kind of incentive because we're talking about a single trial where they may be multiple different drugs, maybe from multiple sponsors or the same sponsor, maybe similar mechanism going after one or more malignancies.

Greg Reaman: I think the agency would be as supportive as possible in assuring efficiency for every good reason. I think the whole idea of master trials and you're probably aware of the Friends of Cancer Research project with the lung cancer master trial where in specific genotypically designed sub-populations of non-small cell lung cancer, patients will receive in a randomize fashion. One, of a variety of a different targeted agents. Could a similar master trial in childhood cancer or in neuroblastoma or rhabdomyosarcoma, Ewing's sacroma, specific sub

types of childhood cancer be done and would that have BPCA ramifications with respect to a written request and a promise of exclusivity? I don't see why it couldn't. I don't think we have any precedents at this point in time. We should be so lucky that we could consider it, but I think the big question is and fortunately the sponsors that have committed to participate in the lung cancer master trial have all agreed to collaborate and to share. They're too close to each other. With agents in this undertaking. Would industry be willing to do that in the setting of pediatric trials? Question back to you.

Howard Fingert: Well...

Greg Reaman: Sorry, Nancy. I don't mean to be... permit me.

Howard Fingert: Just from the few discussions I've had with organizations like Bio, Pediatrics Committee Bio. Others that has been or expressed interest and also getting meeting regulatory clarity about whether or not such participation would satisfy the request. It is a commitment and there is some risk to it.

Dianne Murphy: I can say this because I've some familiaritywith the master trial concept. I think the key here is that a written request, which is how you will get your pediatric exclusivity, is determined before you do the study, usually. And so, what your concern is, what I'm understanding, is a master trial will change during the process but the Written Request won't. Okay.

Greg Reaman: It should convince the design.

Dianne Murphy: Well, that was my point. If you can come in and basically define the master trial and define how it works within that product trial, that could become the Written Request for exclusivity and that should help you get exclusivity. If something happened during the trial that was not foreseen, before you submit the studies, because it's too late after you submit the studies, you have to get an amended written request. The agency is very willing and glad to do that if we see something that's working looks like it's working and we're doing this because we didn't understand something beforehand. We aren't so happy for doing it because you couldn't get it to work for whatever the predetermined endpoint, but you found some little thing down here that maybe on the 13-Sub analysis, then we won't be re- issuing the written request. But definitely, we are willing to work with anybody in trying to define those elements within the written request, I think Greg deserves a lot of credit for trying to push getting this written request, here we can incentivize the industry, because we understand, particularly like you were saying, this is necessary for the the small company.

They have to have something like that to be able to move forward. We really do want to work with those companies and with industry in trying to make sure you get an incentive if it's possible.

Greg Reaman: Nancy?

Nancy Goodman: I'd like to just follow up on comments, Dianne and Howard made. The prospect to the master protocol would be very exciting for pediatric cancer. I think one step we need to make from a regulatory perspective as we're considering that strategy is that written requests need to be made public and this is very important because investigators actually don't have the right to have access to the written requests that shape the trials they are doing. As a community, we don't have leverage to understand better what trade outs are being made in the exchange for pediatric exclusivity and as we get into this reallysophisticated applications of written request, that will be important. In addition, I just want to add that to the extent that written request - I know that many in the FDA think this is something that needs to be considered - to the extent that written requests are now being negotiated side by side PIP's which are fully made public.

Perhaps the original rationale for confidentiality with respect to written request is really isn't as important as it once was. So, I just want to make that one comment with respect to written requests and I also wanted to make a comment with respect to the need to develop drugs specifically for pediatric cancers and to quite get back to the question you made, you raised, Greg, which is what do you do when you're developing a drug for an adult indication? There is not efficacy on the adult side but there are scientific reason to continue considering it for pediatric indications and is there any way we can make it possible for a private industry to stay in the game? One of the big wins we have that will be seen in 2014 comes from CTEP at NCI and Malcolm Smith has been incredibly effective at supporting C14-18 which is a very exciting new drug for neuroblastoma and I think what we've learned from that experience, I hope is that public-private partnerships really can be very exciting.

NCI through CRADA transferred the final steps in drug development through a private company and we really hope that will be a model that can be duplicated. In addition, I hope there will be opportunities for for-profit development of pediatric cancer drugs and that was the impetus behind the creating Hoback. For those of you in industry who are here who may not be familiar with it, the way it works is that if you develop the drug specifically for pediatric cancer and received FDA approval for this drug, this drug has to be - it's for pediatric rare disease, not just cancer - It has to be an NME. Then you receive a voucher from the FDA. The voucher is fully transferable, may be sold to any other entity multiple times and it comes with rights to bump up another drug application from standard review to priority review. We hope that this instrument will create an opportunity for companies to stay in the game and to continue developing those

drugs that may not be appropriate for adult indications and if they're appropriate for kids to develop them for children.

Greg Reaman: Thanks. I just want to go back to your comment about written requests and transparency of them. Just to be sure that even though the PIP's and the written request that are sort of separately negotiated but done so in a parallel fashion aren't always necessarily identical. Even if the written request doesn't made public, I think there is now within the agency and I can say specifically my own involvement has been with the investigator community to get input. There really is an opportunity for as many investigators to get involved and specifically or especially those networks and we do that in open public meetings through the pediatric subcommittee of the oncology drugs advisory committee to get that advice on specific drugs that should be studied using the BPCA mechanism and what those studies should look like.

Even in the setting of a master protocol, I think we could still do that. I'm not sure what do we take to all of a sudden start putting all of the details of the written request on the FDA website. I don't even want to think of what it would entail. Pardon me? A lot of change, as well. We won't talk about. I don't think that's as big in obstacle. Obviously, it would facilitate the things probably in the future as things become more complicated but even despite that, I think there's really an opportunity here. Susan?

Susan Weiner: Yes. I'd like to respond to the question, the case that you post at the beginning which is what should we do about drugs that look as if throwing is going to be a value in a particular pediatric cancer and not a value in the larger oncology community. In addition to the incentive provided by creating Hoback as a provision in FDASIA. There are two other mechanisms that we have involve their organizations worked on in the past. One is something that Dr. Adams and others have discussed which is change in the language of PREA from an indicating being the same in the pediatric cancer as it is in the adult cancer to more current scientific language that would be rephrased, that the pathway that the agent will address was highly similar in adults and kids and then, it would be possible for the agency to apply PREA to oncology drugs which is not possible right now and at the same time, of course to get rid of the orphan drug exclusion which PREA has.

The second idea that we have discussed actively for a number of years was discussed this morning really and really very successful presentation by Dr. Bob Beall from the Cystic Fibrosis Foundation and it's a lesson that I think pediatric oncology really needs to learn that is the private money can create an entity that could license a drug from industry that was of no value to them, in pediatric cancer. As I always like to say, we would grow hair on both. Under those circumstances, private money in collaboration with the clinical resources for children's oncology group and in collaboration with FDA and NCI, we would have a chance to really capturing the potential of the two children that Dr. Helman talked about earlier and those drugs that are particularly hard to develop.

Greg Reaman: Dr. Smith?

Malcolm Smith: Yeah. I would just follow up on that. There are at least two cases now where drugs were dropped from adult development in which NCI has assisted COG and doing clinical trials either to their extent of manufacturing the drug and supporting the trial or formulating the drug with both material provide by the company. I think in both cases, I guess with the concept discussed this morning of the risking a company would never go into a pediatric study from the get go with no signal but if there is a positive phase 3 study, witness example, Nancy described, there are companies that would be interested in taking that and doing the additional steps that are needed to get regulatory approval. I think there are pathways in both public-private partnerships in working with the clinical resources through COG where this is really a possibility.

Lee Helman: While it is happening, it is taken what? Three years? Three and a half years? The speed of which this is taking place is somewhat less than desired.

Greg Reaman: Actually the first example took last longer than three years.

Holcombe Grier: I mean, this is our...

Greg Reaman: This is irrespective of time. I'm sorry, Holcombe.

Holcombe Grier: All right.

Greg Reaman: I think the principle is very sound. The system can work if there's interest in collaboration and it really requires cooperation and collaboration between industry, investigators, the NCI and we're happy to see any application that comes in as a result to that.

Holcombe Grier: I was really going to say this is hard work we deal. In the second instance, there was a trial written four years ago and there was enough cardiac problems that that trial was an incident. Now we know that we can do it but in the meantime, the adult indications all fell apart. We're running against time now because the material that was given to us will in fact, run out. What's happened with all that mind, as hard as this is, what's happened with all that mind is that the NCI is packaging again. The COG is rapidly pouring this trial forward so that we won't miss it and it's happening. It's a positive thing.

Greg Reaman: I would certainly wanted to end on a positive thing and maybe we can open some of the discussion up to the audience as long as we're on a positive note here and would invite any of you with a questions or comments that you would like to make to come forward or to raise your hand and we'll get you to video or you can stay there.

Speaker 1 (Audience Question): Thank you. The comment that was made by Dianne about the impact of the legislation of the EU and thinking about the way the work needs to be done and

rare diseases is in especially on oncology from a global perspective. As you know, in 2013, there were two standard PIP's that where we list by the EMA. One for rhabdomyosarcoma and one for AML. I think coming to that thought about the master trial there, there's great opportunity to have global impact from that stand point and even come to the topic of prioritization. What are the conditions where maybe we should be thinking about early influencing the development of a master trial that can work from the US perspective and from the EU perspective and how it fits into the standard PIP and I'd be interested to hear any body's thoughts on that.

Greg Reaman: Well, I'll provide my comments. I think we actually did explore the concept of the standard PIP which as was described before really requires the elucidation of a full development plan and when you only have a phase one data in adults, I think it's a little bit difficult to define very accurately a full development plan. I think the standard PIP in the master protocol maybe two different things and I think there's great potential in exploring the written request for the master protocol but in speaking with the pediatric investigator community about aligning with the EU in developing a standard PIP's last written request, there was not a great deal of interest and I think just because there just isn't enough information in data to really effectively design what is envision and even with the opportunities for amendments to really work on that. I think our efforts would be better spent in the master protocol.

Peter Adamson: Let me return to unintended consequences and just do a very blunt. I think for childhood cancer drug development, an unintended consequence has really been a delay in the initiation of new clinical trials for children with cancer and an enormous ways to time in resources from any people around the world. Let me just try to put in any living example of what actually happens. As Greg said, at the end of adult Phase 1, companies are required to develop a full development plan, Phase 1, Phase 2, Phase 3. This is before a drug has ever been in a child and maybe before we have any pre-clinical data. You can't do that, it makes no sense but companies are committed to mapping this up and although we may think we know a lot, no one knows that much. It really is, I think at unintended consequences of the regulations and when we evaluate what should move forward, it really is based on the expertise of many people and the sum total of the data.

It's really hard to say, "Today, what data is going to be available? What tools are we going to need? What is our knowledge going to be to map out the full development protocol?" The elephant in the room right now is to be very blunt, BPC and PREA. PREA had been completely tramped by the EMA and it's the EMA that's driving this process globally for childhood cancer growth development and the real concern is we don't want any regulatory body deciding unilaterally and they will argue, it's not unilaterally. They get input but we don't want a regulatory body on making decisions at a prioritization. It's very easy to design a development plan saying, "This is a drug and this is disease." If we were to design a trial in neuroblastoma, this would be Phase 1, this would be Phase 2, this would be Phase 3. Anyone can put that on a piece of paper, but how are you gonna prioritize that drug amongst the landscape of all the

advances being made of different drugs being developed. You can't do it until you get into the clinic and move forward and learn about the drug.

Unfortunately, we've been tramped in the reason to push for a change in PREA as was brought up. It's the trial level, the playing field between the US and European Regulatory Agencies because right now, it's not a level playing field.

Greg Reaman: I would just say that although we may be tramped, there are a number of studies and a number of agents in point in which there are in fact written request that are developed long before there are executed PIP's. Phase 1 studies that are being initiated, have been initiated, have been completed in children before there are PIP's. There are ways to work through it and I think we should make it clear here that the regulatory perceived obstacles are not on this side of the Atlantic. We really want to and we want to work with our European colleagues and we do but I think in have to express some exasperation from time to time about what may be delaying things from their perspective but I think, we have lots of examples of exciting agents that were actually studying here first. In reality, I'm hoping that the real trampers in this setting could result or could effectively be asked in that. Question? Comment?

Speaker 2 (Audience Question): Yeah. I was going to add to that, I think it's an opportunity. I see this not as necessarily a bad thing but a great opportunity for the master trial to really actually be very impactful because if there's an opportunity to now prioritize, develop some master trials so than when the next standard PIP comes along or prepared for that opportunity to really positively influence.

Greg Reaman: I think...

Speaker 2 (Audience Comment): no, no. I realized...

Greg Reaman: I think the master trials and the PIP may sort of be conflict. I'm not sure that I can see...

Speaker 2 (Audience Comment): They are and they're not, because yes, you're right, the PIP is at plan. The master trial is one component of that plan and probably the most important component of it. That's why I think it's a great opportunity for you guys. You guys are the committee...

Greg Reaman: But it's a master trial of a number of different drugs in a particular existing...

Speaker 2 (Audience Comment): I understand that and that's why I'm saying it's a great opportunity for us to actually build that and notice out here, you actually have multiple experts in the field who've come together, created this master trial with multiple companies, with products that can contribute to that that then can actually force the development of the products.

Greg Reaman: I see.

Speaker 2 (Audience Comment): You see what I'm saying? I see it as a good opportunity.

Greg Reaman: Yes.

Dianne Murphy: I know that we all ... It's helpful to have standardization. Okay, that helps everybody. I understand that, but in a rapidly evolving field and particularly in an environment where the science is going to be developing. I would say you should watch out what you asked for? Okay. I'm not bragging on this but I am in a way, the beauty of our monthly meeting with EMA is its sciencet. We don't involve anybody else. Yes, the lawyers can listen, but the scientists are talking back and forth, each asking the other; "I don't understand why you did that?" "Well, is this why you did it." I mean, it is a complete honest open give and take and you need that to be able to keep up with the field and keep moving. This is being recorded, so how do I do say this? When you ask the Food and Drug Administration to develop a standard for anything. They have to go out as a guidance, we're talking two years usually. We're much better off, tying in a fast paced scientific field, a field which is moving quickly scientifically to be willing to not request a regulatory document to get it changed. It's just going to take a fair amount of effort and put everybody's energy into that. What I would say, "Put your energy into the science and the discussion of the science." I'm agreeing with you as far as the goal. I'm just saying be careful about the process.

Greg Reaman: Talked at about …

Robert Iannone: So, I think here, Peter now there's articulating that a challenge with the PIP process is that we're asked to put on paper and come to legally binding agreement around a development plan through registration, some times before we have any day, at a clinical day and then perhaps even at any pre-clinical day to rationale in pediatric indications. A potential solution that's offered to that is here's a standard PIP that could be applied to an indication but again that's not data driven and I agree with you that what we really need is a science that helps us understand for particular mechanism. What's the best way to match on that need with potential of that drug? What I do see though as an opportunity of standardization is the early part of that clinical process. In doing a phase one where we understand how to use a drug safely and what dose as to use it in children and an initial expiration of what some might call 1B or a 2A to look for signals as Lee sort of eluded to even if it's a rare signal to try to understand the science before we venture in to following what they say a standard PIP, I think would be enormous and helpful and from an industry perspective, if there's alignment between agencies that those efforts were count towards something, I think would help accelerate and initiate those trials earlier.

Greg Reaman: But for that to happen, it would really require a change in the European regulations, possibly. I don't think it requires any change in ours. I think the phase on studies

could be done. I mean, it's not common for phase one studies to be done internationally, certainly 1B's and 2A's possibly but I think there's still the opportunity to provide information and important information in what the PIP could eventually look like or ultimately look like with more phase one data and if those phase one studies are done here, because there's no obstacle to doing them. I would see that as another avenue that couldn't be explore.

Robert Iannone: In some cases, you might be drafting the PIP with pediatric data in hand.

Greg Reaman: Right.

Robert Iannone: That might be through and this is going to be done before looking at Malcolm done through collaborations with CTEP to get an earlier start on phase one.

Greg Reaman: Maybe we could just get some...

Dianne Murphy: The sponsor must ask for modification of the PIP. The sponsor must. That's the only way. It's doable. EMA is encouraging and they're more than willing to do it but they don't have the authority, unlike we. They don't have the authority to change the PIP. Sponsors have to ask to change the PIP.

Greg Reaman: Maybe if there are other industry people here that... Howard, of course. But others that would comment on this issue, we'd love to hear about it.

Howard Fingert: I just want to make a comment. I've been thinking about this and observing the process over the past year plus that I've been on the ODAC and I've been impressed with the opportunity to help the children with cancer from the intellectual gathering of resources, both from the FDA, from the advisory groups, from the industry people and from the advocacy community and the parents that happens at the time that these things are happening. I would wonder whether or not there actually could be an opportunity to publish the proceedings of some of these agreements. I mean, it's a rare time that you get sometimes this tremendous intellectual discussion about endpoints, trial designs, regulatory pass. From my perspective, this is personal, these things were all going to be with permission of the company, of each company involved. They're going to be public anyway. There's transparency moves by different large companies and then the Europeans were requiring transparency where the protocol design and the protocol is going to be. We have any way.

It's not like there's some trade secret that's largely behind these gatherings that we're talking about, where this major kinds of considerations are blot to bear and my point here is that, if there's any kind of opportunity that there's intellectual contribution to helping a disease and to help the trial designs and help people move forward, you got to try and think about ways to getting those. I mean, for instance Dr. Pasteur's whenever there's an approval in an adult indication, he will challenge the reviewed group to publish it.

Greg Reaman: It's no longer a challenge. We are supposed to publish, but that's after the approval. So you're talking, there's no restriction on our part except the restriction that's been required because of our relationship with industry to keep this information confidential. There's no resistance to transparency and if a sponsor is interested in doing that, there's really no reason on why the sponsor couldn't do the same thing. Is there a question, I mean there, sorry.

Speaker 3 (Audience Question):Yeah, we could continue for days bashing the PIP process and anyone from the industry here who has done a PIP could jump in. Unfortunately, the key stakeholder for that is not here. Something I want to touch on as part of the objective is there was a presumption there that I think was just brought up about phase one in children. What from the patient's groups, the treating community and the regulators is required to do first in human study as first in kid's study? How do those three groups in stakeholders think about that?

Greg Reaman: Well, we have a long history of doing it. I'll let parents groups or advocates talk about it and investigators.

Susan Weiner: You're talking about drugs that are brought first in human, first in child. Not first in adult and then child. Is that correct? Yes. I think it speaks to the point that I made earlier which is that the taste has to be made. That the scientific evidence is strong enough to risk whatever it is to introduce into that child. Now, whenever, Dr. Smith that I had talked about this issue, he has always said, "But you need a starting dose." The starting dose typically comes from adult studies. By having a starting dose from adult studies in affect, saves that number of children in phase one trial as I understand. If there's a good guess about a starting dose, the science really shows more benefit than risk than I think families especially with kids who have life threatening diseases. We'd be willing to do that. Anything done?

Vishny Eigenmann: Hi. I'm Vishny Eigenmann from Silver Bio, small startup company focused on gene therapy in rare diseases. I just had a comment with regard to the potential parallel assessment of PIP's and written request by the FDA. I know that both agencies had joint evaluation of scientific advice, a joint process. I'm wondering if it would be possible at some point to have a joint process where you go through the PIP in Europe and you have discussions early on with the FDA on the pediatric development from my perspective, I think it would be very helpful. The fact that the PIP process has to be started up at Phase 1, can be a challenge but in my experience, it's actually been very helpful from the industry perspective because it really forces you to think about these issues early on and then helps in the dialog and when we file our IND here in the US, our reviewer actually asked to look at the PIP and I thought that was helpful. We had a good discussion about some of their comments, I just wanted to share that experience.

Greg Reaman: There are opportunities for sponsors to request parallel review of the PIP and the written request. What Dr. Murphy was describing is a non-binding scientific academic interchange whereby the pediatric committee and the FDA and the appropriate review group

discussed the elements and we take turns alternating, actually writing up the results of that common commentary rather than parallel review and providing it to the sponsor. Many of them have found it very very helpful and we now have sponsors actually requesting that and it's facilitated both the development of the PIP and it's accelerated the time by which we can develop written requests and some of that. Other question?

Skip Nelson: Greg, if I can, we have a question from our internet audience.

Greg Reaman: Our internet audience?

Skip Nelson: Yes.

Greg Reaman: This gentleman's had his hand up first.

Skip Nelson: Okay. Well, this came in 45 minutes ago but that's all right.

Will Tree: I'm Will Tree from Janssen. I wonder if maybe we could be informed a little bit about what's happening in the type two diabetes world for adolescents and children with type two diabetes. Currently, there are a proliferation of PIP's and of new drugs out there for a limited population and added a privilege of going to an EMA meeting about this earlier in 2013 and basically what came out of that from the sponsor from the industry point of view is that there were two conditions under which a master type trial would be considered by at least the industry representatives who are there and then that was exactly what was described. A trial in which either drugs from the same class, multiple sponsors or even drugs from different classes, oral hypoglycemics from different classes, multiple sponsors would all be combined into one trial with one standard of care or one control group so you limit that aspect of things which is always good for pediatric drugs.

The two conditions were number one, that in terms of trial design, the EMA and the FDA harmonized completely basically and that we weren't trying to conduct in a very limited population, both in Europe and the United States even though everybody thinks there are so many type two diabetics amongst obese adolescents in this country. Actually there may be a lot but they haven't really been identified and are not being followed in places that we can get to them. The trial design has to be harmonized. We can't be running two different drug development programs. One for Europe and one for the United States. That was the first thing. Okay. Not letting the FDA off the hook there. The second thing is that is in terms of drug approval and even pediatric exclusivity that each arm of the trial from a different sponsor maybe even a drug in a different class had to be compared with the control or the standard of care group in order to get approval, not with each other.

Those were the two conditions that came out of that meeting and I'm just wondering from the FDA's point of view whether you would consider that for pediatric oncology trust?

Dianne Murphy: It's a long discussion and actually, Ron Portman, I'm thinking. No, we have had multiple discussions with EMA about this. One of the issues is sometimes you get to a fundamental difference such as whether you can have placebo control or not that you cannot harmonize on. Other times, there are ways which we don't harmonize because we will think that there's a level of risk that we think the patients are willing to accept that they may not and so, we think we have escape clauses that are adequate and they may not that we can fudge. You're really doing one trial but you're doing two things within that one trial, you're going to get the long-term trial, long term on the product that we think you need to have and yet you can escape early that they think that you need to have.

I'm not telling that I know that they... I'm not in the division, what the final agreements are, but those are the kinds of issues that we do sit down and hash out over the phone. There will be times that we're not always going to agree. t Europe is not the USA and USA is not Europe. Complete harmonization is not likely going to happen. We are going to have differences particularly those reasons I just mentioned. They are not willing to accept placebo in many situations where we are and there seems to be sometimes and maybe the other way, other times where they're not willing to accept risk we think are willing. Yes, we are working on getting all those things so we can do one trial.

Greg Reaman: I think the bottom line part as far as you're not letting the FDA off the hook, it really would be a review division decision. I think type two diabetes is a good model but not analogous totally to the pediatric cancer experience. Skip your...

Skip Nelson: From Michelle Petersen who is a clinical trial manager of Medpace sent an email in and asking particularly about issues of where global trials can't have sites open to all regions. What kinds of consideration can be brought to bear on allowing eligible patients and their families to travel to locations where the site is available and I guess I would just add, not part of her question. The extent to which that's purely an economic decision, whether there's other issues that could be considered? That is somewhat off of the topic but that's her question. I didn't want her to think we weren't paying attention to our email address.

Greg Reaman: Maybe it's a question better answered by an industry sponsor. But I think in general, I'll let Peter answer from a cooperative group perspective.

Peter Adamson: For front line trials, we're fortunate that we have sites, we have 200 sites across the United States. Nonetheless, there are large parts of this country where families have to travel great distances even just to get quality cancer care. Part of the problem is not so much research. Part of the problem is maybe in fact the health care system and the availability of it. What a number of larger centers have for earlier phase trials is through philanthropic efforts, they're able to travel families for early investigational studies. The MCI, the pediatric oncology branch disabled to travel families for studies at the program. With all that said, it is a major burden when

you have to travel with a child and family to get access to clinical research and there are not any, I think easy solutions to that.

Greg Reaman: I'm reminded that we're a little past 2. I wanted... Do you want to make a comment?

Howard Fingert: I just want to.

Greg Reaman: Okay. Well, I'd like to thank the panel but I'd like to actually ask Anne Willis to just make a comment as a survivor childhood cancer, a participant in a clinical trials having received investigational therapy and sort of this, the poster child, if you will of what we...

Peter Adamson: It's poster adult.

Greg Reaman: Poster adult, yes. I'm sorry. Poster adult. What we like to achieve? I mean, it's you that motivates us as well as the children and families who are not as fortunate. We just like your perspective as to whether we're on the right track. What we need to do to get ourselves on the right track because you're talking to investigators, regulators, industry and we'd love to hear from you.

Anne Willis: Great. I have, I think two points that I'd like to make. First of all, we're thinking about drug development. We're not putting drugs to treat disease. We're creating drugs to treat a person and there's a context within which every single patient is receiving that drug and for me, my treatment, I had 18 cycles of chemotherapy. I was in the hospital constantly. I had family, I had friends, I had school and that was taking me away from that which has all kinds of other implications. I was dealing of some of the acute toxicities at the time and at that point, that was a great trade-off and I was happy to meet the trade-off but I think we also need to be thinking more long-term when we're thinking of creating these therapies. I'm now at risk for all kinds of new things because I had cancer and because I was treated and it's something I think about every single day as a cancer survivor. I had Adriamycin, anytime my heart flutters, kind of funny, I wonder. "Oh, am I having a heart attack? Is this happening?" I'm constantly waiting for the other shoe to drop.

To the point that some of the advocates on the panel have made, I think we really need to be thinking about this quality of life issues when we're thinking about clinical endpoint and not just quality of life issues during treatment but also those quality of issues through the rest of that person's life. We're treating these kids but down the road, they are at risk for significant disability and I think that we can do better than that. The other point I wanted to make is I think that patients and parents and survivors need to be included throughout the research process so as we're designing these trials, as we're thinking about research questions and endpoints, as we're

developing these tools, those voices are really important and I think those voices really need to be included from the beginning of the process through the end of the process.

Greg Reaman: I couldn't agree more. We come back... David, did you want to?

David Arons: I want to take off more of your time. I just want to build off what Anne said. We discussed a lot today about tools and about creating a supportive favorable environment for pediatric oncology drug development through the PIP's and regulations. These are all tools. There's a couple of other ways if you are an advocacy organization or representing people to also getting involved. One is thinking pre-clinically. What we've learned from talking to pharmaceutical companies and industry partners is the importance of pre-clinical information. Without that, they're not going to get started. Working with scientist and develop the pre-clinical information as much as possible.

The second is improving our ability to measure response of a drug. In brain tumors, it says a lot of meaning and I'm sure it does in another forms in cancer but we can have the best trials in the world. We can have the greatest regulatory incentives in the world but if we can't measure effectively what a drug is doing to cancer, then it becomes very difficult to reach approval. It's another opportunity for patient groups to work directly with companies, technology companies, pharmaceutical companies, scientist and other patients to work on some of these issues and that's just a couple of other arenas that are very important to oncology drug development.

Greg Reaman: Okay, thank you very much. Again, thanks a million to the panel. I appreciate it. Thanks to all of you. We'll resume at 2:25.

Session Nine
Gene Therapy Trials in Pediatric Patients

Ilan Irony: My name is Ilan Irony, the Chief of the General Medicine branch in the Division of Clinical Evaluation of Pharmacology and Toxicology in CBER. Now there are some controversy this morning about whether this should be called gene transfer or gene therapies. I will allow everybody to use this interchange the way you feel comfortable with the term but I wanted to point out that the goal here is to go from investigational gene transfer or investigational gene therapy to finally approved gene therapies in the U.S. for a variety of diseases including rare diseases.

What we're going to be focusing on in our panel discussion here has a lot of overlap with the other issues that were discussed yesterday, this morning and even in the pediatric oncology panel. It's just issues such as how to appropriate an efficient drug development in a rare disease, issues with pediatric diseases in general, pediatric trials in general and particular, additional protections for children as well as vulnerable populations. Issues related to gene therapies and it overlap tremendously with ages that we face with gene therapy in children.

There is nothing very particular or unique about the issues of gene therapies in rare diseases in pediatrics but what like to focus our attention to the issues that are predominant in gene therapy, particularly the topics of the long term permanent effects of gene therapies and the topics of the long term safety risk and the requirement for long term safety follow up, the need sometimes for investigational device or investigational procedure such as bone marrow transplantation or device inserted gene in the organ of interest, whether it be in the brain, the heart, the liver or the retina for example.

Issues related to small startup companies or patient advocacy group directing or academai directing drug development compared to large PhRMA companies like we've seen in general poor, the pediatric oncology trials.

Before we start, I just want to have a show of hands from the audience. Who is familiar with terms of gene therapies or has participated in gene therapy trials or has considered participation in gene therapy trials? There are a few people but there are a few people here. Who are patients or patient advocates in the audience? Okay. Thank you. This will help us focus a little bit more in our discussion and what we need to talk.

I have two issues before I let the panel introduce themselves and I'll be very quick on this. One is about the issues of patient centric drug development or part of development in our case. In patients are represented at their advisor committee panel for discussions of a drug for approval or not approval but we are starting to get involvement of patients earlier in the process, not just

patients advocating for the need for therapy for their family's disease or their particular condition but in patient networks only but also patients advising us early in the pre-IND period or what is needed, what's an adequate development land, what's in the adequate end point or patient reported outcome for example. We value that opinion or their perspective as part of the overall review of a pre-IND submission or an IND.

The other point that was made earlier in the pediatric oncology discussion about the pediatric investigation plan is the requirement to with formerly a drug development plan for the overall development, not just for a phase run study in children but also for the overall development. We encourage in a voluntary way academic positions, people in academia but also in general. To force themselves to imagine what will be this product's life over the next few years until it gets through a biologic license application for approval or consideration for approval. That's a target for the profile. There's guidance that we refer people to and particularly useful for sponsoring investigators or academic investigators to follow so you can plan and imagine not just the next trail, phase one trail person human but also what will happen next and following that next step until the end.

Of course, things will change as you learn more about the product, as you learn more about the risks and benefits but at least you have a framework to base on, to follow a plan and to create like an imaginary label for the product.

Having said that let me ask the fellow members to introduce themselves. I'll hear from Laurie again.

Laurie Sames: Laurie Sames, Executive Director, Hannah's Hope Fund.

David Williams: Dave Williams from Boston's Children Hospital and pharma cancer institute and we do a number of gene therapies trials.

Anne- Virginie Eggimann: Anne- Virginie Eggimann from Bluebird Bio. We're a small company focusing on developing a gene therapy for rare diseases and I'm leading the regulatory group in the company.

Patricia Furlogh: I'm Pat Furlong, I'm president of Parent Project Muscular Dystrophy. We focus on Duchenne muscular dystrophy.

Katherine High: I'm Kathy High at the Children's Hospital of Philadelphia where I direct a unit, the Center for Cellular and Molecular Therapeutic which has as its goal, the development of new cell and gene therapies for genetic diseases that affect the pediatric population. I'm also a consultant to Spark Therapeutics which was recently spun out of our unit and which will continue the development of those.

Amy Celento: Hello. I'm Amy Celento and I am a patient representative among the Pediatric Advisory Committee. I'm also the vice president of the Cooley's Anemia Foundation and we represent patients that have Thalassemia major intermedia and Thalassemia minor or their traits.

Ilan Irony: Very good. I think the first topic that I want you to discuss yourselves is the issue of the long term or permanent effects. We know that once you give a gene therapy or gene transfer product, you … The facts are going to be long term as opposed to a lot of small drugs or therapeutic proteins that come and go, the effect appears and disappears relatively quickly within hours or days or weeks. A gene therapies is there either to stay or at least to remain for a few years. Some effects may not be seen at all but there are some effects that may manifest themselves, start to manifest themselves after a period of time and that may be long lost and the risk also may be long asked so not just the potential benefits or potential cure but also the potential risk can persist over long period of time.

I want you to consider this and ask from patient perspective, from the sponsor perspective either academia or industry perspective, what would be the considerations to initiate a trial that has a requirement for long term safety follow up. From the patient perspective, the same thing, what are the considerations you would need to think about and consider in trying to participate in such a study?

Amy Celento: I guess I'll start with the patient perspective focusing on Thalassemia intermedia major. The treatment requires lifelong frequent blood transfusions as well as a daily chelation of iron that's accumulated from transfusions and many people are living well past the ripe old age of 15. We do have patient in their 50s and several in their 60s at this point but what happens is that as they mature, they develop many side effects, most of them develop osteoporosis, diabetes, have reproductive issues. Also as patient are living longer, they're encountering bone pain, unexplained, unresolved.

When you look at that in terms of the live spans of Thalassemia, there are side effects that develop as you age. Considering a gene therapy option, certainly there will be the potential for side effects. Insertional mutagenesis is a big question. What cells will be growing, can be in addition to the hemoglobin gene being inserted. It's a risk that patient will balance against what are they facing in terms of a lifelong blood transfusions. It's particularly onerous in terms of missing work, missing school, it's quite a big impact. There will be the opportunity for patient to weight one against the other.

Of course, there's a risk that a gene insertion does not work. They go through a chemotherapy or a modified chemotherapy to reduce the immune response. Again, it's going to be patient by patient but really we advocate for all of the information to be on the table, especially for patients who are younger and who may want to have a family one day. They certainly have a lot of considerations about the impact of chemotherapy as well as again, receiving a gene that could

provide the expected therapy to benefit, it could not and there could be risks down the road but we already know the risks for a lifelong transfusions and all of the complications so it will be up to each individual patient.

Katherine High: We've done clinical trials in a couple of different areas, hemophilia for which another treatment already exists, a good protein therapeutic and also for a rare blinding disorder, Leber's congenital amaurosis or early retinal dystrophy due to specific mutation for which there aren't other treatments right now.

When you talk about long term risks as Amy said, every situation is different and obviously in the setting of hemophilia where there are other options than long term risks assume a different task from a situation where there is no other treatment available. The way that I think about this is that the goal of everything that people do in drug development is to try to make options available to patients and to give patients choices in how they manage their disease.

In a situation like hemophilia where there is a protein therapeutic available, it's interesting if you look back on the history of the protein therapeutic, the first plasma derived concentrates were unbeknownst to the people who were using them and the people who were manufacturing them. Eventually contaminated with hepatitis viruses and with HIV so there were long term consequences to that product that were not anticipated when it was first made.
The situation one could say is similar. In gene therapy, we can define fairly closely what the short term risks are because we know what they are but what about risks that may occur 10 years later or 15 years later or 20 years later?

Then, I think the goal of our work really is to enable regulators to label the product appropriately. We know this risk, we know that risk. We don't have observational data on patients for longer than 10 years. Then, if that becomes a risk that people aren't willing to take, they shouldn't take it if there's another option.

On the other hand, for diseases like Leber's congenital amaurosis, we are at this point, there really aren't other treatments. Then it becomes a question of weighing an undisclosed risk that may occur many years out against the uncertainty of blindness for example. I think the natural history of the diseases becomes then a very important criteria that people consider when they look at potential not yet disclosed long term risks.

Patricia Furlogh: We focus on Duchenne muscular dystrophy, Duchenne is a progressive, debilitating disease, it's x-linked. Families get the diagnosis when the children are two or three, up to five years old. When parents here this, that fatality, 100% fatality sticks with them like lint on a sweater and they look through or at their son in that lens of a diseases that is not only going to take every bit of muscle function from them but their lives eventually.

Gene therapy has been since 1986 and 1987 when the gene and protein product were identified, the holy grail, the idea of replacing a portion of the protein back into these children at some point and time. I think the benefits, certainly in our case certainly outweighs the risks, sorry, because if someone said 10 years down the road, he may develop some undefined condition, I think he would take that risk because sometimes, depending on the age we're talking about, there isn't a 10 years down the road, there isn't a guarantee of 20 years down the road. In the face of that, I think our idea would be to restore that protein as quickly as possible in the diseases course and give us that 10 years or 15 years or 20 years. We will trust that there will be more options available to treat those comorbic conditions.

Anne-Virginie Eggiman: Bluebird Bio focuses on currently two diseases where we have clinical trials ongoing. One is, it's very volatile, muscular dystrophy and Dr. Williams is the key investigator in the trial. It's an x-link diseases also that occurs in childhood and it's a narrative to narrative diseases where a patient cannot metabolize very long chain fatty acids and accumulates in the brain and causes inflammation and degeneration which can be fatal within two to five years.

In our case we have an existing treatment which is transplant so the benefit risk evaluation is slightly different. In our other diseases that we're looking at hemoglobin epitome, bête thalassemia and sickle cell disease. Also patients can be treated by transfusions and/or transplants.

I see one of the comments that was made yesterday is companies that are focusing on rare diseases are committed for the long time and I can say this is the case for focularpio, I think what could be encouraging for patient and families is to know that we're committed to provide long term safety data. For all our trials we're going to follow patient 15 years post transplant.

I think that's encouraging but I also think there's a burden, I think as Dr. Hite mentioned to clearly inform the patients, be it at the informed consent stage or when the product is going to be labeled because we will know a lot more when the product is registered but there will still be a lot of unknown.

I think there's a burden on us to have clear information. For us, for example, it's been very important with our interaction with regulators and the ethics committees, to be very explicit about the benefits and risk of our proposed therapy versus transplant for example. These are my comments.

David Williams: Thanks. We have, I think I have a little to add but just a couple things. Our programs focus on stem cell gene therapies by and large. We're running five trials for those diseases where bone marrow transplantation is the foundation on which the therapy is based,

using the stem cells. The fifth trial is in a cancer indication where we're modulating T-cell for anti-cancer effects.

I agree with what Kathy said. The fact is that you make these decisions about long term side effects based on the best science knowledge that you have. That's quite important but ultimately you have to do the human studies because there's no surrogate really for the longevity that you see in human investigation.

Having said that, as was already pointed out, these indications have known long term side effects, most of the diseases we treat are fatal without some intervention. The intervention that's currently used has known spectrum of side effects, some quite severe, some actually can be fatal. The decision that the families make and the investigators make in these diseases are based on the combination then of known scientific information based on pre-clinical modeling, antecedent human trials were now down the road long enough in gene therapy field so that we do have some track record with respect to understanding side effects that are long term and how to address those. Then, finally, of course the natural history of the disease which I think these discussions become more complicated as you move down the road and you start addressing diseases which are not fatal which have alternative therapies such as thalassemia and hemophilia. I think the discussion becomes a little bit more nuanced with respect to how one looks at these longterm side effects.

Lori Sames: My daughter has giant axonal neuropathy. It's a single gene autosomal recessive neurodegenerative disorder with life expectancy in the late teens or early 20s. Including my daughter, we know of 23 Americans with the disease and I know how to contact another 23 globally. There are no other treatment options for giant axonal neuropathy. We really hit the road running after pulling ourselves off the floor following Hannah's diagnosis. October 1st met our five year anniversary of funding the UNC at Chapel Hill Gene Therapy Center. When Hannah was initially diagnosed, we brought 22 research scientists together in Boston for the world's first symposium on this ultra-rare disorder.

Basically for a day and a half, we discussed everything known about the disease. I asked the scientists to prioritize therapeutic approaches. Dr. Steve Gray came from the UNC at Chapel Hill Gene Therapy Center just to listen. The underlying diseases mechanism, we have more clues and some hypothesis but it takes several years to really elucidate mechanisms in these very complex disorders.

They said to us, "You know, really, your only chance at impacting anyone currently alive with this disease is to pursue a gene therapy approach. Our first study that Hannah's Hope Fund funded was an AAV radavin administration and serotype comparison study. The data were very similar between intramuscular with AAV 9 with retrograde transport to the CNS as well very

similar to the intrathecal ravadin administration and to avoid potential immune response, really it was no brainer for our scientific team to decide to go with an intrathecal radavin administration. Our protocol right now basically, we've funded everything independently in grass roots by a miracle and a lot of hard work and a whole army of people helping us raise money. Essentially, three families and their communities are really helping us do this. It seems the other families are dealing with end stage patients.

We've been able to raise the funds started to run out of money so I approached Kirk Fischbeck, who runs the intramural program at the clinical center at Bethesda and said, "Here's what we've done. We're ready to start a phase one trial. We're working with the regulatory agencies right now but we need you guys to house this out of the clinical center in Bethesda." Thankfully they rose to the occasion.

We really hope our phase one trial will start in March. The NIH scientific review currently has our protocol before them. We should hear from them hopefully on Friday. If we get very positive feedback from them, we'll immediately submit to the FDA and the IRB so because there are no other treatment options, all the families are very eager. You cannot recruit for a trial until you receive regulatory approval so don't ever want to suggest that we've been doing that but we're the only hope that these families have.

When we started funding in natural history study about two and a half years ago, until they heard it from the PI's mouth, that participating in the natural history study wouldn't prevent them from participating in an eventual trial, it was then that they would decide to volunteer to participate in the natural history study. Really, the plan is if an interventional trial were to become available that they wished to volunteer for, they would just withdraw from the natural history study. We have so few patients, it's actually going to turn out that our natural history data are really the pre-treatment data sets, pre-gene delivery data sets that will be compared to the post-gene delivery data sets.

I really wanted to mentioned that because I mentioned earlier that 85% of these 7,000 disorders, most of them, they're 85% are ultra-rare. The funding often is not available for these robust natural history studies but this I think is really a great way to structure it for the ultra-rare disease community. Our families are very eager and there've been no one that they didn't want to learn much more about and eventual trial that we hope is forthcoming.

Ilan Irony: All right. We can stick with you for now. I want to slightly change the approach here to this first question and say, once you insert a gene in a person through a bio factor or some other means, through autonomous cells, those effects are permanent or long term. When an investigator hears that there's some other interfering substance, investigational product on board, it goes on to enroll that particular patient into a trial for a separate new product because they

want to make sure that the assessments that they're doing for safety, for early efficacy are consistent with the effects of that particular product, not the one that was given before.

What are the considerations from a patient's perspective or patient's family perspective versus academic investigator or industry that approach of gene therapy precluding participation in the future of perhaps new promising small drugs or therapeutic protein enzyme replacement or something like this?

Lori Sames: My opinion on that is that it shouldn't preclude them from other investigational trials. Even with siblings, obviously with the same genotype, they could have slow progressing phenotype. We all have compensatory genes. Siblings do not have the same DNA In every disease we've got phenotypic variability even within the same genotype.

It's my feeling that if you participated in a trial and it had marginal benefit that puts you at the scale of the missense mutation cohort for the next investigational trial that you participate in. I think that's a rational approach.

David Williamson: I think that's a very complicated question and I think you'll get a different answer from sponsors that are industry based versus academicians versus family groups or patient groups. I would say probably as an investigator at an academic institution, I would not automatically say that we should eliminate enrollment in other trials but I would be very cautious about it because I think it, in the trials that we're talking about, the early phase human trials.

As you've already pointed out, one of the points of an early phase human trial is to gather as much information about efficacy and toxicity as we can. Once you start overlaying onto that additional experimental modifications, it becomes quite difficult I think or could become quite difficult to sort those two things out but I can anticipate in our studies where we have some years of experience in certain patients and enough patients worldwide that we begin to understand the toxicity profiles that one could cautiously layer on another experiment approach in some instances.

Anne-Virginie Eggiman: I'm not a physician so it's hard for me to comment on whether the patient we will treat will be able to go on additional trials. What I can say there is or are clinical trials. We do have an exclusion criteria which says that we cannot exclude patient who have received gene therapy before.

I think what that really means for us because we use lenta-bio vectors which are integrated into its permanent treatment or long term treatments, what's important for us is to maximize efficacy because we have a onetime treatments where factors of safety where we really do try to maximize and optimize our manufacturing process for example to optimize the number of copies of a genes that we can get into the cell so we're mindful that if patient may not have other options

afterwards that they get the best that they can when we treat them so I think that's important. I think maybe that's it.

Patricia Furlogh: I think of these rare disorders like Duchenne and others where there are no options whatsoever. What seem to me like we have to be cautious, allow for opportunities. I'm wondering if this will get into novel clinical trial design where it is certainly understandable with a gene therapy approach who'd want to limit your cohorts so you can understand clearly what that approach means and is and what potential issues would be involved in the approach but I think then opening up a trial to compassionate use for others who have so few options that may have not responded to an earlier therapy is really going to be important.

Families with debilitating diseases watch every single day while their children, that person that they love, loses something, whether that's strength or cognitive ability. I think they deserve as many options as possible. Clearly the communication around benefit and risk has to be there and has to be solid and both and all parties need to understand it but I think it's really important in these debilitating conditions to have options to participate.

Katherine High: I would just make two comments. One is that I take your point about waiting for the next thing that's coming along in the pipeline but for some of these diseases that Pat said for neurodegenerative or retinal degenerative conditions, people don't really have the luxury of waiting to find out the next thing that may be available five years from now because by then there may have been permanent changes that make that not really an option for them.

Second, I would say that because a lot of the diseases we work on are genetic diseases that certainly what motivates some people to participate is not the thought that it will make their own case of hemophilia different but rather that one of their grandchildren who's affected will benefit from their participation in the research. I think as we've said, every case is different and every situation is a little bit different.

Amy Celento: In the case of thalassemia and maybe sickle cell and some other single gene hemoglobinopathies. I didn't mention before but bone marrow transplantation is a potential cure for thalassemia. Depends on the match and the age at which the procedure is done.

When you look at gene therapy as an option, if it fails, if the patient remains transfusion dependent, I guess I can't really say definitely that the gene therapies would have failed but if it really did not provide an effective cure, I would certainly not want to limit patient from pursuing other options and it is quite possible that they could have a haplo-match BMT as an adult and I certainly wouldn't want them to be precluded from that option.

I do want to mention because it was indicated before that maybe having thalassemia or another disorder is not fatal. It actually is still considered a fatal disorder. These treatments that are

available are incredibly challenging and those patient still die from thalassemia related complications, typically heart disease or liver disease from iron overload. I think I'm looking up the fact that it's not as an obvious degenerative disorder as some that we're discussing today. However, it really is still degenerative. People develop all these comorbidities and it is most likely what will kill a thalassemia patient.

Ilan Irony: All right. Thanks. Also related to the issue of the long term effects, my last question related to this topic is when you have a small drug, particularly for an ultra rare disease such as giant axonal neuropathy for example, where you have 23, perhaps 40, 50 patient that can be studied, the safety database is very limited for a review of application, for biologics license application for example or for an N.D.A. We know a lot about the product by the end of phase three. I know about, even in this very limited data set, they know about the efficacy, whatever can be learned about efficacy, we learn about the short term and relative medium term safety because those patients had been followed for years after they were keeping this ultra product or therapeutic protein.

Unlike those products, in gene therapies sometimes the long term adverse effects, the safety, the cancer is consequence of insertional mutagenesis can metastasis only after a few years, four, five years. How long do regulators, not just F.D.A. but European regulators, Japan or Australia would need to wait until we get a more complete picture of the safety to be able to balance risk and benefits, assuming that those diseases are really a mathematical needs in their favor or life threatening diseases.

In those considerations of increased benefits balance in the framework of whatever else is available from their transplantation or other therapies, how do we put this into the equation of the unknown of the long term safety risks?

Amy Celento: I'm not sure I'm qualified to speak to that but I will say again, as a parent, as a patient, it really is going to just depend on their own tolerance of risk. It could be they want five years of data. It could be that they want 10 years of data and it could be that they're willing to take the chance of, "Well, maybe I have a risk five years from now and so be it. I'll adapt and overcome." I'm not sure.

Katherine High: I'd like to say that I'm not qualified to answer this either but again, as I've said before, I think the goal in the work of drug development is to enable everyone involved including the regulators to label the product accurately. If the label needs to say that the risk of this after 20 years is not yet known, then it has to say then.

For some of the work that we've done, we have long term follow up for decades in large animals and for long periods of time in humans as well but do we have 50 years of follow up? No. I

think that's really the point of that all of that information has to be reflected accurately in the final labeling process.

Patricia Furlough: In the natural history of Duchenne muscular dystrophy, it's predicted that these young men will go off their feet, that they will have trouble breathing, need evasive ventilation, non-evasive ventilation, potentially evasive ventilation and they will likely die of heart failure. That's known and that's the natural history of the diseases with a mean age of death right now of 29.

I think if we balance the list of potential 50 years from now or 20 years from now of developing a tumor, if that would be the risk, I think that any parent of a child and likely the young men themselves would sign on to those extra added years, certainly if they're accompanies by increased or expanded function, I think we'd all sign on. That's not to say what may happen in the future isn't going to be difficult but life with Duchenne is fairly difficult anyway and we'd all be willing to assume that risk.

Anne-Virginie Eggimann: Thank you. From my perspective, a couple of things - I think if you want to encourage innovation and development of gene therapies products, I think five to 10 years safety on data on all patients at the time of the BLA filing, maybe a high five and maybe a hindering, companies wanting to go into that field.

I also think that, by the time you get to the other, you usually have a spectrum of duration for our patient. The patient you treated earlier will have a little bit longer than the latest patient. I think the way we think about it is we think of a two year period full up as something reasonable for the majority of the patient knowing that you have average, a good number of patient that would have much more than that. Some of the concept that we know would like that to consider is something that's been discussed in the you and I think is discussed here as well is having an approval and maybe a restricted population while you provide safety data as post approval.

That concept of adaptive licensing, I know it has to do with benefit/risk and it's not just safety but that concept of limiting the risk in the restricted population unless you gather more safety information in the long term follow up which for example, in our case, we're committed to gather and little by little, maybe the agency can be more comfortable to expand a little bit the indication while still being transparent in the label.

David Williamson: Again, I think most things have been said. I'm struck as a practice in hematologist, oncologist every day by the fact that when I walk onto the transplant floor that that field is by use of both radiation and allocating agents, clearly putting patients at long term risk for secondary tumors and other bad complications you heard this morning, cardiomyopathy and so on, so having said that, I think it's like everything else. It's going to be sort of disease specific because that thought process by the FDA and by the European regulators, I'm sure will be

informed by the severity of the condition and by the quality of any animal modeling data that is relevant. Some is not relevant, some is.

As Kathy said, long term studies and models for sure, I think it's not so different from other drugs. Only as you point out and the fact that it's permanent changes but I think that can be taken into consideration and a thoughtful approach which I'm sure will be the case with the FDA.

Lori Sames: My panelists have spoken to long term effects but I think I will just share. Someone texted me a press release that just hit this morning. The data submitted to the EMA for Glybera which is the first gene therapies approved in Europe was published in *Human Gene Therapy*, establishing that the immune response they saw to capsite and gene product did not diminish expression as the one year point. I just wanted to share that short term good news.

Ilan Irony: All right. I want to keep the conversation with you and Dave now on the issue of funding for this overall development of the product from completely different perspectives. It's a different model than a drug company funding the whole development product. For example, from the perspective of Bluebird Bio or some of the other startup companies. In terms of efficient networks and mobilizing patient families to look for source of funding or other networks or researchers for example, how do you manage, how do you foresee something that can lead to efficient development of product?

Lori Sames: From the share of hands we saw early, they refute patient advocates in the room so I'm guessing the vast majority are from industry. One of my goals today is to excite you about the field of gene delivery. I think you need to take this amazing therapeutic and business potential back to your boardrooms and really start discussing translational programs in the field. The gentleman spoke yesterday about comparable drug for E.R.T. for Pompeii, I said, "Oh, my god, there are 6,000 that have no treatment options. How'd you convince your board to go for that?"

It comes back to a business model and intellectual property and the vector that we're using is AAV9 and there is a patent holder for that. We're using a self-complementary captive which is more efficient so it's double stranded versus single stranded. Talking over my head. I'm not a PhD. I'm a bachelors degree and passion, heart and determination, that's my acronym.

There has to be a business model and there has to be a rational sublicense agreement, I'm told industry standard for an I.P. holder when you're not going to be involved or incur any expense for anyone utilizing your I.P. is typically three to five percent. There are many groups working on, I know, efficient vectors to the CNS which will be competing products so I think there's great opportunity there and I just want to share that. There are many devastating diseases where a gene therapy approach is very rational.

You can align with an advocacy group like Hannah's Hope Fund and it's a very clear path and Sever has been amazing to work with and very helpful and very responsive so I just, it's a niche. It's a great opportunity and I think the time is now where we can really impact devastating childhood diseases but also have a very favorable business model. I know people are throwing around if it takes the insurance company estimates to care for a child with Batten diseases from birth to death is $2,400,000 then the price tag for a gene therapies could potentially be half of that per patient so all these things are being worked out. I don't have the bandwidth right now to follow Glybera and what's happening with that in Europe but it's a great opportunity that I hope you all bring back to your executives.

David Williamson: I won't speak to much to the pharmaceutical approach, although it's heartening that after what was over a decade of lack of interest from biotech and PhRMA that there's clearly an uptick in interest from both big PhRMA and biotech companies in this therapeutic modality. Others can talk to that. I'd like to speak to two different parts that are not that then. One is the role of the NIH in funding gene therapy research.

Several years ago, the American Society of Gene Therapy put together a committee that made recommendation to the NIH about how better to support research in this field. The recommendations were published in *Molecular Therapy*. I think they make a lot of sense and they actually are similar to a program that NHLBI. has, called the Gene Therapy Resource Program or GTRP The way that works is there is up front, a review by an informed, knowledgeable panel of diseases experts and gene therapies experts and production experts of the proposal that then extends through pre-clinical development, manufacturing, certification and clinical trial.

Those milestones, there's a release of funds within a ministry of review but without another peer review which is always deadly to allow the project to go forward. In our hands actually has worked reasonably well with reasonably speeded reviews and released some money and so on and so forth.

That's one thing and I think that's a program that could be worked at more broadly at the NIH and these things. The other is patient groups so certainly in some rare disease, Chronic granulomatous disease is an example, Fanconi anemia is an example. There are others, I'm sure, where the parent groups or disease groups have actually generated enough money to support both pre-clinical development of research. In the case of CGD, actually clinical trial funding and that's another approach.

I guess the extreme example of that is Genethon in Paris, in France which is muscular dystrophy like, Jerry's Fund like of philanthropy groups that actually runs their own GMP facility, runs their own laboratories and has been very aggressive at funding multiple gene therapies trials

around the world. That's, I think, a great example of how the diseases specific parent groups and philanthropy groups can have a large impact in the field.

Anne-Virginie Eggiman: Thank you, Dr. Williamson. I think I can echo some of that is, I think there is a lot of important communication between academia and industry. For example, in our case, so our Cevo's particularly gifted in getting funding so we haven't have too many issue. There is a good momentum right now for gene therapy, it can work out there in Europe. I think that was mentioned but I think we were successful in getting funding because a lot of the early trials that were done by academia using previously lenta-bio vector director that we improved, really supported and provided clinical evidence or permanent area of evidence for what we're doing.

I think it's important to keep funding of academia for gene therapy because even though there's a good momentum at the moment, I think it really helps to have proven your evidence and this is a good setting for getting this innovative data.

With regard to private, public partnership, I also think that for example for C.C.A.I.D., this is very important to get new born screening and it's something that is challenging for us so the reason it's very important is because if patients are often misdiagnosed because of the diseases presents can be compounded with ADHD or other mild symptoms in the beginning. If they're not diagnosed early enough, the progress very rapidly. They can potentially they can progress too much to benefit from treatment. That's something we are working very closely with stakeholders as much as we can. It's challenging but it's something we would like to participate in constructively if we can.

Also, we're were collaborating with Dr. Ashler at MGH in Boston and Professor Sober in France to create a consortium to gather information on ALD and we talked a lot about natural history. This is part of our collaboration but we're going to provide our input to create a database and gather as much information as possible on ALD in general which includes also adult patient.

Ilan Irony: All right. Thank you. For the sake of time, I just want to go to one last topic and then open up for public, for the audience participation. I'd like to ask Dr. Hi about the issues of immunogenicity. We know that the purpose of the gene therapy is to express in a protein of interest, the protein may be different and mutated protein or the absence of a protein in the body of someone with Leber's congenital amaurosis or hemophilia or another disease and it will trigger an immune response.

In addition, there will be some immune response to adenovirus or adeno-associated virus that are vector to carry this gene of interest. How do you handle this in terms of eligibility, risk benefit of this, when do you consider approaches to immune suppression which investigation for this kind of purpose and with their own potential risks.

Katherine High: Okay, so thank you for that extremely complicated question. (Laughing) I think many people in the room probably know that for gene therapy products, you have to consider two classes of responses. One, is the responses to the vector itself, and the other to the gene product which the vector encodes.

Let me make a pass first at the immune responses to the vector. Again, now there are two things to consider. One is that there can be pre-existing antibodies for example to AAV Vector so there can be a humoral immune response that you have to worry about and a cellular immune response to the caps that you also have to worry about.

For the antibodies, what we have seen in the work that we've done is that if the vector is injected directly into a target to shoot such as a subretinal space or into skeletal muscle, the antibodies don't really have a chance to get to it but if you are trying to target something where you have to pass the vector through the circulation like the liver or heart muscle, that these antibodies will become essentially for you, an efficacy issue because you will not be able to get past them and a person with antibodies, the vector will be neutralized and there will be no effect.

There was one question in there about what should we include people in trials who have these preexisting neutralizing antibodies. To me, the answer is, if you're going through the circulation to deliver the vector, no, you cannot include them because they will not be informative for the study of the drug. The other component of that immune response, not the humoral response but the cellular response can result in late manifestations not late as we've been talking about but several weeks in, can result in immune response so if your target is the liver, you may get a transaminase elevation and for that, some groups have shown that a short course of steroids will dampen that down.

That would be the situation of when do you introduce an immunomodulatory agent. To me, this is a clear case where the failure to introduce an immunomodulatory agent at the right time in the right doses will obliterate any prospect of efficacy. Then, it's reasonable to consider and people have adopted several different strategies for investigation under those circumstances and one of them for example, simply that investigators don't enroll into the study people who are unable to go a course of immunomodulatory therapy.

Again, that makes your trial maximally informative and probably increases the likelihood than an individual patient would have a positive effect. It also increase the likelihood that they will have some ill effect related to the immunomodulation. Again, it's a complex area but it can be dealt with.

The area of immune response to the transgene product itself, I think that one of the first questions that everybody's interested in is can we take everything that we know from protein replacement

therapy and immediately apply it in the realm of gene therapy. For example, people with large gene deletions who are at more at risk for an immune response to a protein replacement therapy, are they also more at risk for an immune response to the transgene product and gene therapy? I mean, logically one would predict yes. I think there's data out there to support that but is there a one to one correlation? We probably don't know the answer to issues like that.
If anybody else would like to add to this very complicated area.

Ilan Irony: All right. I would like now for the sake of time to open this for the audience for you to ask questions of the panelists or myself. Dr. Nelson will hand the microphone here.

David Williamson: Sorry, I just had forgotten to add in the discussion about finances. Actually, I should have. One approach that we've taken in rare diseases is to develop international consortiums and share the cost of product development, of preclinical development product production and then for … That's the ticket if you will to pay to get into the clinical trial and then the clinical trial is the same protocol across all institutions.

It has the benefit of reducing the cost per institution. It also has the added benefit in rare diseases allowing us to ask a scientific question and get the answer much more quickly and move onto the next question and actually that's been quite effective in our gene therapies approaches.
For that actually, it's been important that most of that money has come from institutional investments in the science.

For instance, at our place, the institution invested a large amount of money to get us going and other institutions involved in our consortium, they did the same.
That's really important to know that institutions are committing resources to this product development.

Howard Fingert: I'm Howard Fingert. I was in a prior panel. I wanted to ask if anybody in the panel or the audience has been able to make steps forward to deal with this issue that was discussed earlier about crossover to other treatments.

There have been proposals on the statistical side for approaches like what's called IPCW, inverse probability of censoring weighted analysis. I don't really know, it's a Cox model approach that accounts for the censoring that happens when the patient drops out, let's say with a follow up on the trial. I don't know if there's been any kind of success, steps forward, whether or not the agency, very powerhouse in my view, a powerhouse of resource, in terms of statistics and statistical approaches have been able to help with better clarify because these kind of things would help us in the industry to support trials.

It's one of the limitations with these kind of prowl designs, with the current common vanilla statistical approaches really are problematic, let's say. Understanding there's different alternatives to statistical approaches would be informative.

Ilan Irony: I'm not sure if any of you would like to tackle the question. I can take a stab at this and then feel free to … I think you've heard before that we are open to all kinds of different proposals for alternative designs and alternative statistical analysis of data. in particular, in rare diseases where every patient counts and we don't discard any information, every bit of information is valuable, safety and efficacy. We want to use as much as possible, the information.

We've seen lots of proposals for adopted design certainly in small drugs, crossover designs are feasible and are a way to save on patient and have a tighter variability around the information that you get but it's not something that I think we can … It will depend on the particular conditions of the trial, the database that is being … How many patients are available and the appropriate certification for that particular statistical approach for us to be able to review the data and understand what the message is from those data.

Charlie Richards: This is Charlie Richard. I have a response to Lori Sames and a question for you. You said, "Gosh, I just want to make sure large PhRMA are aware of all the incredible opportunities here and to be aware of all this." I think having been part of two very large due diligence efforts at large PhRMA looking at the idea of in licensing or opening up large gene therapy units, I think I can assure you there's incredible excitement about that and especially amongst the basic scientists that work at these large PhRMA.

The problem has always been the commercial proposition that stopped both of those in their tracks. Now, I can't really say more. I don't work at these companies any more so I'm probably not at liberty to say much more than that but I can assure you, it's not the incredible excitement that the promise holds. That's pretty aware to people.

The question I have to do with you has to do with your giant axonal neuropathy trials since you're ready to submit to the F.D.A. you said pretty soon. You said you just had 23 patient in the U.S., you had limited funds, you don't really had the kind of funds that Duchenne or C.F. had. Did you actually do a big pre-clinical tox program and find a way to get that funded? That's often part of the value of death for small people before they go forward or are you just going to wing it? Are you prepared to say how you're going to do that?

Lori Sames: Yes, we raised about $6,000,000 in five and a half years so we were able to fund the preclinical and the GLP. tox and GMP vector manufacture. It's our little miracle in the making hopefully. It can be done. We've got two challenge grants by Doris Buffett's Sunshine Lady Foundation. We went to Pepsi Refresh grants. Those were each $250,000 a piece.

Actually an 84 year old woman learned of us from our local news and a few days later she was watching the *Early Show* and saw Doris Buffet on. She was being interviewed and she wanted her last check to bounce, she wants to give away her fortune before she dies.

This 84 year old woman wrote a letter to her on our behalf and Doris Buffett hand wrote a letter back and she said, "Have them reach out to me and be willing to consider doing a matching challenge grant. They had a local fundraiser planned." Little did she know, we conducted about 30 a year.

I sent her a three page later, sent her a copy of our video entitled *Faces of GAN*. It shows the progression of the disease. Three days later, her assistant called me and they offered us a six month, $500,000 matching challenge grant. At first, I thought it was 18 months. I said, "Do you mean February 2011." They said, "No, 2010. You've six months." We reached out to everyone we knew and we asked them to create their own project team and figure out how they're going to raise money for Hannah's Hope Fund in the six months window. We raised $622,000 in six months.

We started to run out of money again, contacted her. She gave us a $450,000 match.
We we're running out of money a third time and that's when I approached the clinical center here at the intramural program to house our trial. We were able to fund it independently. The goal is we're hoping since we have such a small patient population that we can just get a right of use to the three patent holders because we also have a small synthetic promoter that was patented by a student in Denmark, so really three I.P. holders are involved in our product.

I think there are a few groups pushing to go forward in the clinic with 89, we don't know if we're going to be first in human or not but we'll certainly share all of our human date with the I.P. holders. The goal is to either get a right of use or a sublicense agreement. If this works, we negotiate with carriers any profits that would ever be made would come back to our charity, Hannah's Hope Fund, to continue to work on more efficient vectors.

Again, this is just the central nervous system. We have to treat the peripheral nervous system eventually, trying to work on the molecule approach for that. We're trying for sustainability because we can't keep going to our family and friends and say, "We need another $1,000,000." It's about safety, efficacy, control and sustainability.

That's the model that we're trying to employ to make this happen, to keep being able to drive the research and get children impoverished around the world who have this horrific diseases treated or receiving gene delivery, I should say.

Ilan Irony: I want to ask the panel and perhaps a public or whoever had the kind of experience before and the issue of in addition to the gene therapies risks and potential benefits. Sometimes

as we look to the relative administration can be evasive, can be an intrathecal, in the heart or in the brain.

They use the devices that required to achieve that kind of relative administration or the procedures that are somewhat invasive, like you need to have to have sometime a transplant associated with this gene therapy protocol with their own risk of transplants. All the integrated those risks.

It's not just a gene therapies product itself. If you were given the skin or the blood but the device at training, how much innate of assessment with the device if anyone has experience with this in order to bring this product forward in development and eventually to marketing.

David Williamson: I think it's as many of the things we talked about today; it's a calculable part of the equation. Probably the simplest example is our format for stem cell gene therapy is harvesting of stem cells. That can be done in several ways and the risk of that are separable from the risk of the gene therapy part but additive that the individual, the subject in the trial has to go through those risks to get to the point of having modification of the cells before they get it back.

I think in all of these cases, one has some prior knowledge of those kind of risks in general because these are usually built on preexisting methodologies that have been used for some time in whatever the disease is and that specific field. I don't know if anyone else wants to …

Katherine High: I can just say that for the trial that we've done in early retinal dystrophy, the administration of vector involves going to the operating room and going under general anesthesia and getting a subretinal administration of the vector through an already approved device but to obviously then the patient has to understand or his family, the risks of general anesthesia, the risks of the surgical procedure and so forth in order to give informed consent but as David said, "These are all fairly well quantified risks."

Will Tree: I just … Is this on? Yes. This is Will Tree from Jansen so I have a naïve question. I don't know butkus about gene therapies. I realize that you have a lot of different disease, different routes of administrations, different risks of immunogenicity, et cetera but it seems to me like especially when we're talking about longterm safety implications and risks.

We need to collect data. I know this Is going on for at least several years now, maybe even a decade or more but probably relatively few patient who've received gene therapy For all these many diseases.

Has there been any effort on the part of the NIH or anybody else to form a registry of gene therapy recipients from all diseases to go forward and try to look at the natural history of receiving gene therapy for whatever diseases with whatever vector and in whatever route of

administration. Seems this is a golden opportunity to do something at least in the United States which is rarely, rarely done which is create a national registry and follow patients.

David Williamson: It's a really good question and I think it's a good time to think about this again. The answer to the question is there is some attempt to do this through the NIH Recombinant DNA Advisory Committee and it's requirement for registration of gene therapy trials through what's called GeMCRIS. There is a database of patients who've received the recombinant DNA products. The FDA requirement currently is to follow patient for 15 years. That data is being collected but I think we've actually, our group was just talking about this that it's a not international in scope.

Therefore, there probably is room for that approach. As is always the case, one of the issues is how do you fund such an approach? I think that might be a complication but I think it's worth an attempt to try to figure that out. I think the investigators in the field, I think would be quite open to this kind of registration for future safety analysis and so on.

Lori Sames: To add on to this as far as needing cooperation in the field, for homozygous deletion patients, it's very hard to model immune responses. Even with enzyme replacement therapies for example, I know in the Pompeii scenario, kids who had some level of functional enzymes that weren't predicted to have an immune response did. It gets very complex but I know all the different gene therapies centers are really working to figure out a solid, safe immune tolerance protocol or immunosuppressant protocol to deal with immune responses and trying to prevent them.

I think the field is still very segregated and working in silos and there's not a sharing of data. I did host a meeting in Salt Lake, the American Society of Cell and Gene Therapy conference was there in May. I think there were 17 P.I.s that attended. I think we met for six hours. Really, not a great deal came out of that. A couple papers by PI in the room had been published since then. Their findings were submitted for publication but they weren't shared.

Not to be a negative Nelly, but I think the field is still behind and we can all advance so much more quickly and have a better chance at safety and efficacy, in particular with dealing with immune response if we really collaborate and share information and ideas to really help us all advance more quickly.

Ilan Irony: More questions from the audience? I just want to thank everybody from the panel from coming over here to participate and contribute into this very interesting discussion. I can tell I've learned a lot from this. I learned from the two days to be here, the other sessions as well. Thank you very much.

Dianne Murphy: If you all can hang around for about 15 more minutes, we're going to have each of the session chairs come on up right now and provide a five minute summary of their takeaway messages for today. If you can hang out to the very end, I'm going to tell you about some future meetings that we'll be announcing in the upcoming years. Anne Zajicek, I hope she's here. She said she would be. Greg, otherwise it can be really short. There's Greg. Skip, I saw you so I knew you were here. Oh, here's Ann and Eli.

Okay. Ann. You are our first lead. If you would start us off and with that … Carrie, can you give me a high five, we're running five minutes each? Okay. If you would give us five minutes, as I said, takeaway messages, take forward, what do you think was useful about today's meeting?

Ann Zajicek: I think I would go with the subtopic, if that's okay. I really appreciated people coming, especially the patient advocates. I know they have a lot on their plates so I appreciated them coming and sharing what was going on with them.

Bullet point number one, need for regulatory level or regulatory quality data, needed to be coming from academic centers and need for a culture of research and the lack of equality of academic research and drug regulatory drug development research quality. Again, the need for data that it is auditable, that's performed under good clinical practice, good laboratory practice, good manufacturing practice and so on.

Point number two is the embedding of training and also to a certain extent, fundamental research In the clinical trials. We've been trying to do that with the pediatric trails network, embedding trading in there. In terms of the fundamental research which came up yesterday, I think that's under the aegis of NIH generally speaking but embedding for example, outcome measures, trial outcome measures, secondary outcomes in clinical trials is helpful. Patient out care advocates certainly needed for setting the research agenda for determining what they feel to be … Excuse me, clinically relevant outcome measures, determining what could be validated as end points, I think would be certainly helpful as well as protocol development.

The point was well taken this morning that it's fine to draw seven cc's in a red top tube every minute for PK but it's not going to happen or having people come overnight for visits when they have sick children come and that's not going to work, either. Having the advocates enmeshed in the program as well.

Patient enrollment is a chronic problem. There's a couple ways of managing this. Point number one is to again involve the patient care advocates and let them know or other families know there are clinical trials available for their children. Good project management in the last few years have become more and more aware is really key. If you don't have a manager who is managing

the whole project then things really just fall off the wagon. The clinicians are busy, they have other things to do. Enrollment just goes down the drain.

The issues about patient reported outcomes including the relationship between pediatric patient reported outcomes and then observer reported outcomes was needed, that was common around this morning.

One comment that was made yesterday was about phenylbutyrate. Oh, my gosh! It makes the entire retrovirals look like ice cream so the fact that it took a while for the urea cycle people to realize that the people simply want taking the phenylbutyrate and then a new tasteless product was approved in the last year or two. I think maybe including in the patient reported outcomes, actual ability to take whatever the product is, I think might be nice to roll that in there.

A point was made by Gayle and by Betsy Peterson this morning about devices and she used the common about stents, those cardiac devices and I'm sure this will be talked about extensively tomorrow but the issue of materials around that, is it just a matter that the pediatric devices are smaller than the adult devices, were they completely different, do they have to grow with the child and so on and so that's a whole material science question.

Then, last comment about the strong relationship between pharmaceutical industry and advocates for developing protocols, outcome measures, that kind of thing was very helpful. One last thing, there seemed to be three layers of issues. There was the foundational research and then there was the natural history studies and then there was the drug development.

I guess in the enmeshment at some level of the … Excuse me, the fundamental research being performed by NIH or other granting agencies and then a natural history studies being performed either by advocacy groups … excuse me, or the NIH and then development of the drug. I guess that would include pretty much all parties involved including the advocacy group, the pharmaceutical industry, the NIH to a certain extent, especially with the NCAP program and then the FDA. That's what I got.

Dianne Murphy: Thank you. That's great.

Ann Zajicek: We're about out of time right?

Diann Murphy: Thank you very much, Ann. Skip?

Skip Nelson: I like to stand up when I talk. I was an immunologist and critical care doctor and the residents knew if I sat down the rounds would never end so I keep walking. Back in 1977, this will take less than five minutes. I won't be doing the whole history of back … Back in 1977, when the national commission framed the ethical guidelines for including children in research,

the described the category where we're talking about benefit to the children as just like clinical decision making.

The framework that they gave where the risk must be justified by the possibility of benefit and that balance of risk and benefit must be similar to the alternative they explicitly framed as being similar to clinical judgment. Now, I don't want to reinforce what people are often concerned about, called therapeutic misconception but being in research is being the same as getting treated by your physician but on the other hand, I think it does reinforce the idea that was, I think echoed

In a lot of the conversation both in the second panel and then in the conversation that this judgment if you will about the benefit that's worth achieving and the risk that one is willing to take and the uncertainty surrounding that decision, that it's something that really has to take place among all of the various parties to that conversation. Those parties in that conversation in many ways are in fact of people in this room, they're the parents, children if they're capable in participating, the clinician investigators, the sponsors that are putting the protocols together, the FDA that's looking at that, saying, "Go ahead." Includes the IRB's. They haven't been here but I think this is a conversation that has a big impact on how they should evaluate those criteria for deciding whether a protocol ought to proceed.

In many ways, I see what happened and what happened both in all four panels has really a manifestation of the need for that conversation to be happening. What impressed me most is yes, there's a lot of that conversation is already going on and you've heard about it in different areas with different relationships and different advocacy groups working with different investigators and the like and doing great things.

What I take away from that is more of that needs to happen and it needs to be shared. There's a lot of experience in making that happen that other people can learn from but at least from my perspective, in terms of this assessment of how we understand risk and benefit and the uncertainty that that's a conversation that has to be had among the people that are most effected by that decision and that includes those who are in fact enrolling in the trials, the parent's who are making those decisions, the investigators, the sponsors and the FDA around those issues. That's what I took away as the main message.

Dianne Murphy: Thank you. Greg.

Greg Reaman: Okay. What I heard was I think what I've known for many, many years is the importance of patients and advocates and families and the importance of their input.
In clinical trial design and now, even more into end point selection and particularly in the realm of quality of life and oncology, quality of survivorship, which is really a long term evaluation process and the importance of selection of patient reported outcomes and the need for the development, validation of appropriate instruments for simple things that could be assessed by

patients themselves, which is challenging given the various developmental stages of children who are study subjects but things that could actually be augmented by caretaker or observer, response as well.

I also heard that the current development program of new drugs in childhood cancer which really begins with patients in the very latest stages of their illness. As always, traditionally informed and lead to subsequent plans for earlier stage settings but I think there are opportunities to look at not just approving drugs in the front line setting which takes many, many, many years because of our randomized control studies which take four or five years to accrue and another four or five years to analyze from the standpoint of evaluating end points which is usually event free or relapse free survival. There may be ways to really look at measures of clinical benefit in addition to or in some cases instead of overall survival.

I think it was clarified that risk in pediatric cancer trials is very much a disease and stage specific. I think the agency has been somewhat risk averse in studies where there may be an intervention in a front line therapy approach where the outcome is currently very good and just being concerned about erosion of some of those results by the addition of a new agent or the substitution of a new agent and maybe subtracting something that's known to be effective.
I think there was obvious concern about the differences in process procedures of the international regulatory agencies, notably the EMA and its process.

I think we shouldn't give the impression that we are in any way bashing the fifth process because in reality, at least for my perspective, I think it was brilliant that there was a requirement to have these pediatric investigation claims. They maybe too early but to actually have a requirement for even beginning to think about evaluating promising agents in children, I think was step in the right direction.

I think there are ways to deal with some of the differences and perspectives that don't necessarily require anybody lobbying for legislative change in either Europe or the U.S. I think the last thing we need is one more guidance. I think I would like to suggest that we have a little bit more time with our pediatric cluster calls and providing common commentary to see if we can demonstrate to advocates, patients, sponsors, all of the stakeholders, investigators, that we can in fact work this out.

I think the discussion around a master protocol was very good because the whole idea of competing products and how we prioritize given the rare nature of the disease and the small number of patients and the excellent outcome of most patient so looking at a master protocol situation of same in class agents in genotyped tumors across a variety of diseases if they're focused on the same target or else looking at different targets or targeted agents in the same diseases would be a very efficient way of dealing with that.

It would also be a good way to require even more cooperation, collaboration internationally. The role of public/private partnerships, I would like to think that more of them could become a reality as we see agents that may hold potential relevance for children disappear because they fail in the adult indications for which some of these promising targeted agents were developed.

I think an end of one gives me some hope but it's very limited and I think we just need to have more of a commitment. What I've also heard was the importance of philanthropy and I think in pediatric oncology, we've been fortunate to have had very significant support from taxpayers in the form of cooperative agreements with the NCI that have funded networks.

I think we've been excellent stewards of those funds and have accomplished a great deal but I think those funds are beginning to decrease. No matter how much you have in the way of funding, you never have enough. You always need more and hearing the story of the CF Foundation always just makes me admire what they've done. I think if we could do that in all rare diseases in children, it would be great.

Dianne Murphy: Thank you very much, Greg. Ilan?

Ilan Irony: All right. What I've heard from my panel and from the discussion about the long term effects or permanent effects of gene therapies or gene transfer is that some of this requirements are taking for long term follow up are taking stride by patient community by the investigators. They are accepted in them. They need to participate.

It depends on the disease, the decision to participate in a clinical study depends on the disease, what alternatives there are and what's at risk and benefits of the alternatives and what is specific benefit that we're aiming at with the gene therapy product in clinical consideration, in terms of this long term effects, both beneficial and as far as harmful effects, precluding patients from participating in other trials.

Again, this is a decision that is made disease by disease, patient by patient or family by family. The truth here is to be transparent on what to expect and what providing informed consent on the potential benefits, what's known from pre-clinical, what's known from other trials are similar with a different type of retrovirus or genovirus for this type of condition or for similar conditions and be very transparent, very complete in the informed consent process for patient. It's not necessarily something that precludes patient from participating in future studies or the drugs, whether small drugs or other gene therapies but it's something that is to be considered on a case by case basis.

In terms of how much is needed for marketing application, again, what I heard very clearly is that it's a matter of being transparent in appropriate and clear label. If we see that magnitude of effect on a particular life supporting or life changing that type of benefit is such that the benefits

outweigh the risks, at the time, we see the marketing application. Some of the uncertainties of the long term risk can be dealt with appropriate labeling and continuing the work of pharmacovigilance and post marketing requires studies for the long term safety.

In another message that I've heard, very loud and clear is the importance of alliances between investigators and academia between patient groups and investigators, between patient groups and PhRMA or small startup companies. It's essential that those interested to have a common interest in particularly rare disease to have some alliances both in terms of recruitment, both for participation and clinical studies, as far as funding, which is something in particular, invoking other multinational partners not just U.S. but also other academic centers in Europe or elsewhere for the purpose of recruiting patients and funding, having a single protocol that can result in faster and more efficient development.

In a similar vein, this multinational effort should be extended to registries for all patients treated with gene therapies so we can sect out particular effects or particular retrovirus or particular antivirus or AAV or AV in addition to the effects of transgenes for the effects of different diseases. To combine those numbers in addition to having in the U.S. for GeMCRIS in an international level would be beneficial for all U.S. as well as for all international partners.
The last thing that we discussed was the issues of immunogenicity.

Immunogenicity related to transgene, the gene of interest triggering an immune response and how to deal with this in terms of future treatment or neutralization of the fact of this beneficial effect or immune response to the factor to the AV which is relatively common in population, people have been exposed to then unassociated virus and some subclinical infections with those viruses in those viruses and how this would in certain circumstances effect the eligibility of the patient to participate if there's something that's going to be given systemically through intravenous course for example versus something that's given immune privilege site such as subretinal space or intrathecal for example. That decision will be effected by the broad administration and eventual risk benefit overall.

Some of those issues related to the uncertainties of the associated procedures that for example, bone marrow transplantation that needs to be done in conjunction with gene therapy or the safety of device, that even if it's approved for a particular product or drug infusion and may not have been approved for gene therapy. That has to be included in adequate informed consent process not just informed but the process of informing patients and families.
I think this is quick summary of what the oral discussion was.

Dianne Murphy: Thank you very much.

First of all, I want to thank everybody for being here this long. But why are you here? What need is there to sit through this? Why did you get your cars cranked up this morning to come in the

cold, five degrees, three degrees weather? Because you want therapies for children and you want therapies for children with rare diseases.

Here's what I took out of this meeting. (What we at FDA have to do soon and what we'd have to do for the future.)

It's important to recognize there are different types of networks. What we're talking about is people product development networks. The specific goal of these networks is to provide data, be it natural history, clinical trials, pre-clinical that we can provide that will result in product labeling that has information on how to use this product in pediatrics.

There cannot be a different standard for industry and academia. FDA has one standard and that's hard in rare disease, it's hard period but particularly hard in rare diseases and that's why we're here, to make sure we have robust information that you as a parent or as a patient will feel confident that your participation results in something that is worthwhile and we call that product labeling.

The input of families is critical and the various advocacy organizations are needed to help us move this field forward by providing data that FDA can use and that is representative of the entire population, because those of you who come here often are a select population and the most motivated. We need you to help make sure that all voices within the effected population are heard. We realize that time is the enemy in many situations.

How do we move forward?
-First, we need to expand the development of pediatric networks, that are capable of doing pediatric product development.
Second, we need the leadership that understands how to get this done. Adeliverable can be, or we hope it will also be, publication. But as far as the agency is concerned, the deliverable is information that goes into a product label. That's what we're meeting about. That's what you want.

The rest should flow if we get these networks up and running. We have this kind of leadership. We have this kind of commitment. We should be able to get the rest of this to flow, including protocols for natural history studies that will help us in this endeavor.

The third thing is access to and sharing of data. It is the basis of the future. It has to be available for everybody. We have to think about ways of making it available and protect patient privacy as far as genetic data is concerned. The government, the FDA, sponsors, we need to continue to work, to leverage patient and families and their knowledge in developing our

protocols and our risk determinations. We, the FDA will continue to work to harmonize with Europe and the rest of the world.

One last thing, having been at many institutions, of a variety of types, it's always struck me how some people think they can do pediatrics. I would say that one of the problems that has existed is the assumption that people know enough about pediatrics and they know how to conduct pediatric trials when they really don't. We need pediatric expertise in all levels. By that I mean, pediatric expertise needs to be in industry, it needs to be at FDA, it needs to be in IRB's, and it needs to be in hospitals with research centers of excellence. We need pediatric expertise just like we need the families. They are providing the kind of risk assessment and clinical input that has slowly evolved. It's much better than it used to be. People know they can't go into a neonate and take out 10 cc's of blood nowadays, but it's been a long haul and it will continue to be a long haul.

Also, we will try to move forward with three particular events. One, Terrie just agreed to help and I know that the session leads will help providing a summary that we'll post up on the Office of Pediatric Therapeutics web page at the FDA We'll link it to the Center for Drug and Biologic web pages, NIH/ NICHD'ss web page so that there'll be a summary and by summary, I do mean summary of the points, mostly of what the session chairs have said.
Second is that we will be announcing, but haven't announced it yet through the *Federal Register*, we have so many interested people that want you to know, that coming September of 2014, FDA will be sponsoring an investigators training workshop. There'll be no cost to it.

You have to get yourself there. We're not going to pay for any of your travel or any of that stuff but we are going to provide the expertise so that if you as an academic researcher or any other kind of researcher of pediatrics trials, want to know what needs to be done to get something that FDA is willing to accept and review and hopefully meet our standards, we will be putting that in an announcement about that meeting. Look for that for sometime in September.

Then, as you heard, we have a report to Congress due in 2016. It's part of FDASIA's requirement that we report on the success or difficulties, what they are and how is the pediatric program working. This needs to be reported to Congress in 2016. Before we do that, though, we need to have a stakeholders meeting. It won't be focusing just on rare diseases. We will be having another stakeholders meeting and we hope to be able to get input as to what progress we have made and where we need to go forward in the future.

What'd I say wrong? Is it, "We have a date?" Okay, January, 2015 for that meeting. Again, thank you very, very much for being here. We hope to see you again involved and we hope to be able to have more products come out for children and it can only occur with your participation and contributions. Thank you very much.

[Meeting Adjourned]